Organocatalyzed Enantioselective Synthesis of 2-Amino-4*H*-chromene Derivatives

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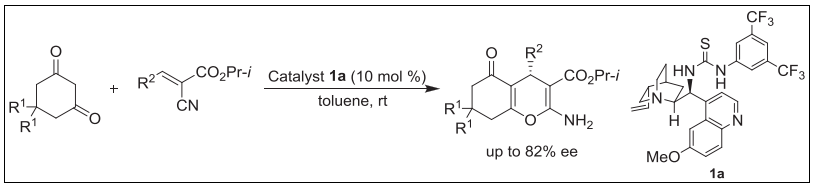

Optically active 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates, 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, and 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles were synthesized. Using cinchona alkaloid-derived bifunctional catalysts, the corresponding 2-amino-4*H*-chromene derivatives were obtained in high yields and moderate to high ee values (up to 82% ee) from the tandem Michael addition–cyclization reaction between 1,3-cyclohexanediones or 1,2-cyclohexanediones and (*E*)-3-aryl-2-cyanoacrylate or alkylidene malononitrile derivatives.

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INTRODUCTION

Chromene is an important structural motif that can be found in many natural products, such as tocopherols, flavonoids, and anthocyanins, which possess many biological activities [1]. Moreover, polyfunctionalized chromenes also play an important role in the field of medicinal chemistry because these compounds frequently display various biological activities, such as anticancer, anticoagulant, spasmolytic, diuretic, anti-anaphylactic, antibacterial, and fungicidal activities [2]. Because of their biological significance, recently, there has been considerable interest in developing high enantioselective methods for the synthesis of these compounds, especially the 2-amino-4*H*-chromene derivatives [3–10], and several organocatalytic methods have been reported in recent years [4–10]. Our group is interested in developing enantioselective methods for the synthesis of substituted pyrans and thiopyrans [11,12]. Herein, we wish to disclose a detailed study of the synthesis of 2-amino-5,6,7,8-tetrahydro-4*H*-chromene derivatives.

RESULTS AND DISCUSSION

Our approach for the assembly of these 2-amino-4*H*-chromene derivatives was based on a tandem Michael cyclization reaction between a cycloketone nucleophile (1,3-cyclohexanediones or 1,2-cyclohexanediones) and arylidenemalononitriles or 3-aryl-2-cyanoacrylates. The cyclization reaction between cyclohexane-1,3-diones and other 1,3-dicarbonyl compounds and benzylidenemalononitriles in the presence of a suitable base was used in the literature for the synthesis of racemic 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles and similar derivatives [13]; however, the enantioselective version of this reaction was seldom explored [8a] prior to our initial study [12].

Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates. Because Brønsted base is a good catalyst for the racemic reaction [13], it is conceivable that asymmetric induction may be achieved in the synthesis if a chiral Brønsted base is used as the catalyst [14]. Thus, using 5,5-dimethylcyclohexane-1,3-dione (dimedone, **2a**), and (*E*)-ethyl 2-cyano-3-phenylacrylate (**3a**) as the model substrates, we first screened some common chiral bifunctional Brønsted bases (Fig. 1) as the catalyst for their ability in inducing the desired enantioselectivity in the synthesis of ethyl 2-amino-7,7-diemthyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4a**). The results are summarized in Table 1.

As is evident from the data in Table 1, when quinine-derived thiourea **1a** (10 mol %) was used as the catalyst in toluene at room temperature, the desired chromenone product **4a** was obtained in an excellent yield of 92% (entry 1). The formation of **4a** was confirmed by comparing its ^{1}H and ^{13}C NMR spectroscopic data with those reported data [3]. The ee value of this product was determined to be 72% (entry 1). Similarly, excellent yield of **4a** and good ee values were obtained with the dihydroquinine-derived thiourea **1b** (entry 2) and cinchonidine thiourea **1c** (entry 3). When quinidine thiourea (**1d**) and cinchonine thiourea (**1e**), the pseudo-enantiomers of **1a** and **1c**, respectively, were applied under the aforementioned conditions, slightly lower ee values were obtained for the opposite enantiomeric product, but the yields remained high (entries 4–5). In contrast, when quinine (**1f**) was used as the catalyst, the desired product **4a** was obtained in a high yield (94%), but with a much inferior ee value (22%, entry 6). Similarly,

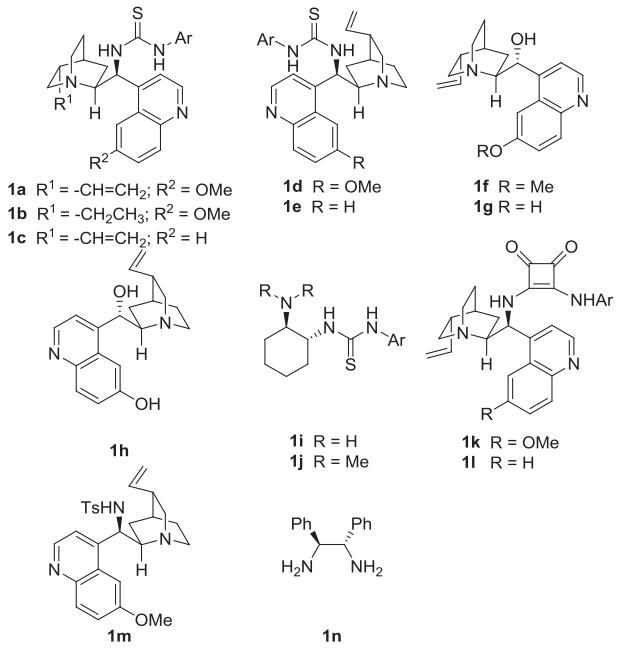


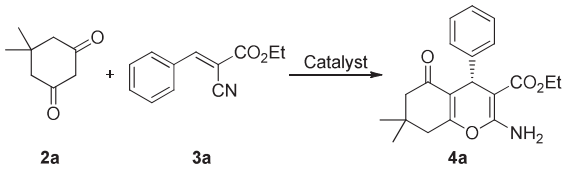
Figure 1. Structure of the catalysts screened in the study [Ar = 3,5-$(CF_3)_2C_6H_3$-].

cupreine (**1g**) is also a highly reactive but poorly enantioselective catalyst (entry 7). These results indicate that the thiourea moiety is essential for achieving good enantioselectivity in this reaction. As an additional evidence of this, the Takemoto thiourea (**1j**) [14c] also led to a much better ee value of **4a** (57% ee, entry 8) than **1f** and **1g**. When quinine squaramide (**1k**) was applied, the product was obtained in 61% ee (entry 9). Thus, this screen identified quinine thiourea (**1a**) and dihydroquinine thiourea (**1b**) as the best catalysts for this reaction. Because **1a** is more easily accessible than **1b**, 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, dimethoxyethane (DME), and ether (entries 10–13). Other common organic solvents, such as tetrahydrofuran (THF) (entry 14) and CH_2Cl_2 (entry 15), led to slightly inferior ee values of the product. Additionally, slightly lower product yields were obtained in ethereal solvents like DME and Et_2O (entries 12–13). Thus, toluene was identified as the best solvent for this reaction.

Table 1

Catalyst screening and reaction condition optimizations.[a]



Entry	Solvent	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	**1a**	1	92	72
2	Toluene	**1b**	1	93	72
3	Toluene	**1c**	1	90	70
4	Toluene	**1d**	1	91	62[d]
5	Toluene	**1e**	1	90	66[d]
6	Toluene	**1f**	1	94	22
7	Toluene	**1g**	1	91	14
8	Toluene	**1j**	1	84	57[d]
9	Toluene	**1k**	1	91	61
10	Xylene	**1a**	1	91	71
11	Benzene	**1a**	1	90	70
12	DME	**1a**	1	86	71
13	Et_2O	**1a**	1	85	70
14	THF	**1a**	1	90	68
15	CH_2Cl_2	**1a**	1	93	62
16[e]	Toluene	**1a**	4.5	92	79
17[f]	Toluene	**1a**	4.5	74	77

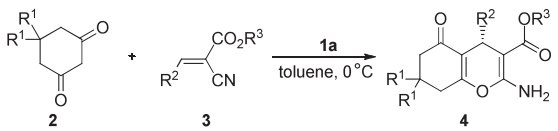
[a]Unless otherwise indicated, all reactions were conducted with dimedone (**2a**, 0.10 mmol), (*E*)-ethyl 2-cyano-3-phenylacrylate (**3a**, 0.12 mmol), and the catalyst (0.010 mmol, 10 mol %) in the specified solvent (0.5 mL) at room temperature.
[b]Yield of isolated product after column chromatography.
[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.

Secondly, the influence of temperature on this reaction was 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 16). Further decrease of the reaction temperature to −15°C showed no enhancement in the ee value but with a further decrease of the reaction rate (entry 17).

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 alkyl groups on the (*E*)-2-cyano-3-phenylacrylates (**3**) have some effects on the enantioselectivity of this reaction: The ee value of the product **4** 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 because of the steric effects [10]. Because 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 **3** 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 electronic effects of the substituents may be able to change the hydrogen bonding capability of the cyano and carbonyl groups in **3**, which, in turn, leads to the changes in the product ee values. A similar phenomenon has been observed before in a similar reaction [7a]. The position of the substituent on the phenyl ring also affects the enantioselectivity. While *meta*-substituted **3** gives 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 because of 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%

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

[a]Unless otherwise specified, all reactions were conducted with cyclohexane-1,3-dione (**2**, 0.10 mmol), alkylidenecyanoacetate (**3**, 0.12 mmol, unless otherwise indicated, R^3 = *i*-Pr), and catalyst **1a** (0.010 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]R^3 = Et.
[e]R^3 = Me.
[f]Determined by HPLC analysis on a ChiralPak AD-H column.

and 76% ee, respectively. 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 have some beneficial effects on the enantioselectivity but not on the reactivity (entry 3 vs. entry 17).

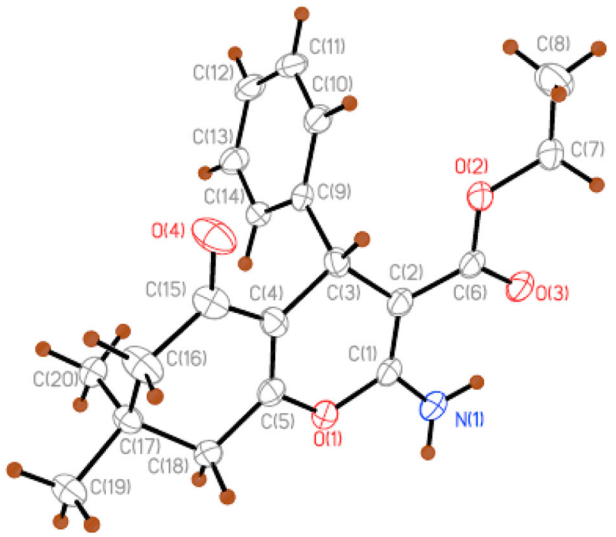


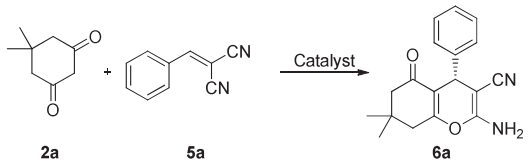
Figure 2. Oak Ridge thermal ellipsoid plot O-substituted drawing of compound **4a** [15]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The stereochemistry of the newly formed stereogenic center in the product **4** was determined by X-ray crystallographic analysis of compound **4a** (Fig. 2) [15]. According to the X-ray data, the *S*-configuration is assigned to the major enantiomeric product formed in this reaction.

Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitirile. We then focused our attention in synthesizing 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives using 1,3-diones and benzylidenemalononitriles [16]. Using dimedone (**2a**) and benzylidenemalononitrile (**5a**) as the model substrates, we first screened the catalysts. The results are summarized in Table 3. As shown in Table 3, all the cinchona alkaloid-derived thiourea catalysts **1a-e** (10 mol % loading) were able to produce the desired product **6a** in high yields in much shorter reaction times as compared with that of (*E*)-ethyl 2-cyano-3-phenylacrylate (**3a**, Table 1). However, only low enantioselectivities were obtained (entries 1–4). Takemoto thiourea catalyst **1j** also gave the desired product **6a** in only 18% ee (entry 5). It should be pointed that the opposite enantiomer was obtained as the major enantiomer when catalysts **1d-e** and **1j** were used.

Table 3

Catalyst screening and reaction condition optimizations.[a]



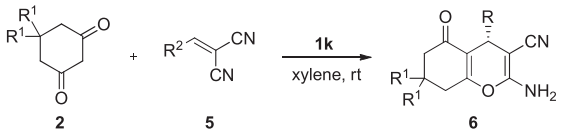
2a **5a** **6a**

Entry	Solvent	Catalyst	Time (min)	Yield[b] (%)	ee[c] (%)
1	toluene	**1a**	25	97	31
2	toluene	**1c**	25	97	31
3	toluene	**1d**	25	94	26[d]
4	toluene	**1e**	25	96	24[d]
5	toluene	**1j**	25	91	18[d]
6	toluene	**1k**	25	98	60
7	toluene	**1l**	25	97	58
8	xylene	**1k**	25	96	62
9	CH_2Cl_2	**1k**	25	99	52
10	THF	**1k**	25	98	58
11	Et_2O	**1k**	25	92	56
12[e]	xylene	**1k**	60	96	62
13[f]	xylene	**1k**	180	88	62

[a]Unless otherwise specified, all reactions were conducted with dimedone (**2a**, 0.10 mmol), benzylidenemalononitrile (**5a**, 0.12 mmol), and the catalyst (0.0025 mmol, 2.5 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 Chiral IB column.
[d]The opposite enantiomer was obtained in excess.
[e]The reaction was conducted using 1.0 mol % of the catalyst.
[f]The reaction was conducted at 0°C.

Table 4

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



Entry	R^1	R^2	6	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	Ph	**a**	1	98	62
2	Me	4-FC_6H_4	**b**	1	96	54
3	Me	4-ClC_6H_4	**c**	1	96	53
4	Me	4-BrC_6H_4	**d**	0.75	98	54
5	Me	4-CNC_6H_4	**e**	1	92	31
6	Me	4-$NO_2C_6H_4$	**f**	0.75	94	36
7	Me	4-MeC_6H_4	**g**	1.5	91	64
8	Me	4-$MeOC_6H_4$	**h**	2.5	74	60
9	Me	3-BrC_6H_4	**i**	1	93	0
10	Me	2-BrC_6H_4	**j**	1	95	51
11	Me	3-$MeOC_6H_4$	**k**	1.5	86	45
12	Me	2-$MeOC_6H_4$	**l**	1.5	82	51
13	Me	2-thienyl	**m**	2	90	48
14	H	Ph	**n**	4.5	63	52

[a]Unless otherwise specified, all reactions were conducted with cyclohexane-1,3-dione (**2**, 0.10 mmol), benzylidene malononitrile (**5**, 0.12 mmol), and catalyst **1k** (0.0010 mmol, 1.0 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 ChiralPak IB column.

Nonetheless, when a quinine-derived squaramide catalyst **1k** was used, compound **6a** was obtained in a much improved ee value of 60% (entry 6). Similarly, an improved ee value was also obtained with the cinchonidine-derived squaramide catalyst **1l** (entry 7). These results show that cinchona alkaloid-derived squaramides are much better than their corresponding thioureas for benzylidenemalononitrile substrate in terms of enantioselectivities.

The solvent used in this reaction was then further optimized using the best catalyst **1k** (entries 8–11). A slightly higher ee value of 62% was obtained in xylene (entry 8); however, common organic solvents CH_2Cl_2, THF, and Et_2O all led to slightly lower product ee values (entries 9–11). When the catalyst loading was reduced to 1.0 mol %, there was no change to both the yield and ee value of the product, although the reaction took a little longer time for completion (entry 12). Lowering the reaction temperature to 0°C did not affect the ee value of the product but had a negative effect on the reaction rate (entry 13).

The scope of this reaction was then evaluated under the optimized reaction conditions using different benzylidenemalononitriles (**5**) and cyclohexane-1,3-diones (**2**). The results are summarized in Table 4.

As the data in Table 4 show, this reaction exhibits a very similar trend in terms of the effect of the benzylidenemalononitrile *para* substituent on the product ee values as (*E*)-ethyl 2-cyano-3-arylacrylates (Table 2): An electron-withdrawing group on the *para* position leads to a lower product ee value (entries 2–6), while an electron-donating group (methyl or methoxy) on the *para* position

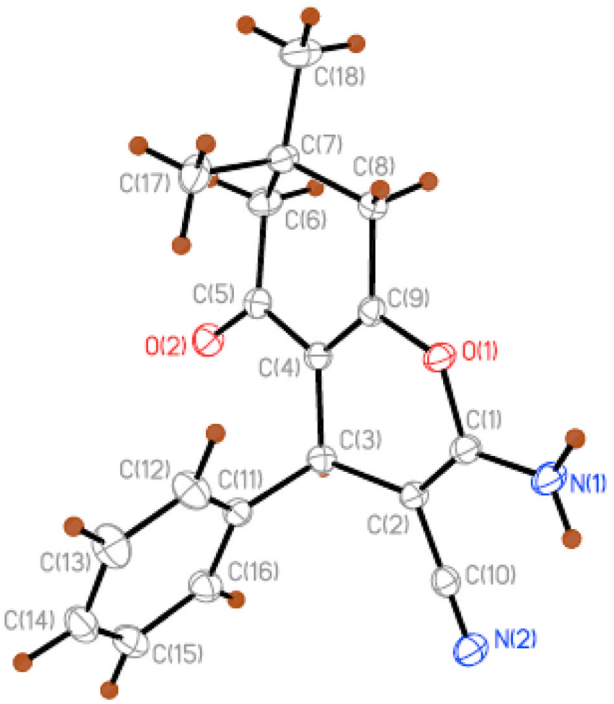
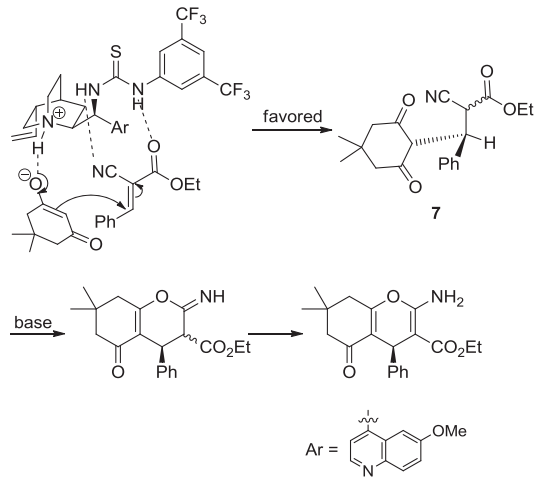


Figure 3. Oak Ridge thermal ellipsoid plot O-substituted drawing of compound **6a**[17]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

leads to a better ee value (entries 7 and 8). An electron-withdrawing or an electron-donating group on any position other than the *para* of the phenyl ring lowers the enantioselectivity of the reaction (entries 9–12), and the effects are prominent as compared with (*E*)-ethyl 2-cyano-3-arylacrylates [7a]. When the heterocyclic thiophen-2-ylmethylidenemalononitrile was applied, the reaction yielded the expected product **1m** in 48% ee and 90% yield (entry 13). Besides dimedone, unsubstituted cyclohexane 1,3-dione also gave the expected product in 63% yield and in 52% ee value (entry 14).

Scheme 1. Proposed favored transition state for the formation of **4a**.

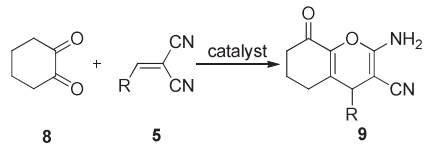


The stereochemistry of the newly formed stereogenic center in the product **6** was determined by X-ray crystallographic analysis of compound **6a** (Fig. 3) [17]. According to the X-ray data, the *R*-configuration is assigned to the major enantiomeric product formed in this reaction. Apparently, according to the X-ray data, compounds **4** and **6** have the same absolute configuration, which indicate that the transition states responsible for the formation of these compounds are similar.

A plausible mechanism is proposed to account for the formation of the major enantiomer in these reactions. As depicted in Scheme 1, the formation of (*S*)-**4a** may be explained by the proposed favored transition state, in which the enolized dimedone is closely associated with the quinuclidine backbone of the catalyst **1a** through ionic interactions, and hydrogen bonding and the orientation of (*E*)-ethyl 2-cyano-3-phenylacrylate (**3a**) are controlled by the thiourea moiety of the catalyst via hydrogen bonds. The attack of the enolate from the back onto the *Re* face of

Table 5

Synthesis of racemic 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles.[a]



Entry	R	5/9	Solvent	Catalyst	Time (h)	Yield[b] (%)
1	Ph	**a**	toluene	DABCO	27	75
2	Ph	**a**	toluene	DBU	30	43
3	Ph	**a**	toluene	Et_3N	38	67
4	Ph	**a**	toluene	K_2CO_3	48	29
5	Ph	**a**	toluene	$NaHCO_3$	72	0
6	Ph	**a**	CH_2Cl_2	DABCO	24	71
7	Ph	**a**	THF	DABCO	28	74
8	Ph	**a**	EtOAc	DABCO	27	64
9	Ph	**a**	acetone	DABCO	29	51
10	Ph	**a**	EtOH	DABCO	30	61
11	4-ClC_6H_4	**b**	toluene	DABCO	24	73
12	4-BrC_6H_4	**c**	toluene	DABCO	30	59
13	4-CNC_6H_4	**d**	toluene	DABCO	23	45
14	4-$NO_2C_6H_4$	**e**	toluene	DABCO	22	64
15	4-$CH_3C_6H_4$	**f**	toluene	DABCO	25	67
16	3-BrC_6H_4	**g**	toluene	DABCO	20	65
17	thiophen-2-yl	**h**	toluene	DABCO	26	79
18	$CH_3(CH_2)_5$	**i**	toluene	DABCO	32	39

[a]All reactions were conducted with the indicated arylidenemalononitrile (**2**, 0.30 mmol), 1,2-cyclohexanedione (**8**, 0.32 mmol), and the catalyst (0.030 mmol, 10 mol %,) in the specified solvent (1.5 mL) at room temperature.
[b]Yield of isolated product after column chromatography.

3a gives the intermediate **7**, which undergoes further base-catalyzed cyclization and tautomerization to give (*S*)**-4a** as the major enantiomer. The formation of (*R*)**-6a** using **5a** and catalyst **1k** may be interpreted in a similar manner.

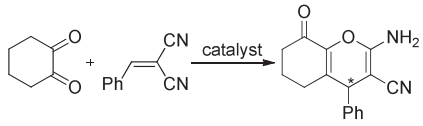
Synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles. 1,2-Diones are highly reactive compounds and have found many applications in organic synthesis [18]. Nevertheless, they have been seldom used in organocatalyzed reactions [19]. Previously, we and others have demonstrated that 1,2-diones can be enolized and used as a nucleophile in organocatalyzed reactions [19c–g]. On the basis of these findings, we envisioned that cyclohexane-1,2-dione could be used as a potential Michael donor in a tandem Michael addition–cyclization reaction with benzylidenemalononitriles for the synthesis of 2-amino-8-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles, an isomer of compound **6**, for which a general synthesis was not available.

In order to demonstrate the feasibility of this reaction, we first studied the racemic version of this reaction. We adopted cyclohexane-1,2-dione (**8**) and benzylidenemalononitrile (**5a**) as the model substrates. As shown in Table 5, when the reaction was carried out with 10 mol % 1,4-diazabicyclo[2.2.2]octane as the base catalyst in toluene at room temperature for 27 h (entry 1), the expected product **9a** was isolated in 75% yield. Similarly, 1,8-diazabicyclo[5.4.0]undec-7-ene, Et_3N, and K_2CO_3 can also be applied to catalyze this reaction (entries 2–4), although lower yields were obtained. However, when a weak base $NaHCO_3$ was applied as the catalyst, no desired product could be obtained (entry 5). Further screening of the solvents revealed that toluene (entry 1), CH_2Cl_2 (entry 6), and THF (entry 7) are good solvents for this reaction, while EtOAc, acetone, and EtOH (entries 8–10) are worse ones. Several substituted benzylidenemalononitriles were then applied as the substrate under the optimized conditions. As shown in Table 6, acceptable to good yields (45–73%) were obtained with benzylidenemalononitriles that contain either an electron-withdrawing substituent (**5b-e**, entries 11–14) or an electron-donating group (**5f**, entry 15) at the *para* position. A benzylidenemalononitrile with a *meta*-bromo substituent (**5g**) also led to good results (entry 16). Heterocyclic thiophen-2-ylmethylidenemalononitrile (**5h**) gave the highest yield of 79% of the desired product (entry 17). Alkylidenemalononitrile **5i** also reacted to produce the expected product **9i**, although the reaction was sluggish, and the yield was lower (entry 18). However, other 1,2-diones, such as butane-2,3-dione and 3-methylcyclopentane-1,2-dione, do not yield the expected product (data not shown), with the former gives no product at all and the latter some unidentified products.

Based on the earlier results, we then developed an enantioselective synthesis of these 2-amino-4*H*-chromene derivatives using chiral Brønsted bases (Fig. 1) as the catalyst. Again, compound **8** and benzylidenemalononitrile (**5a**) were, as the model substrates to screen, the catalysts and optimize the reaction conditions. The data were collected in Table 6.

Table 6

Catalyst screening for the enantioselective synthesis of **9a**[a].



8 **5a** **9a**

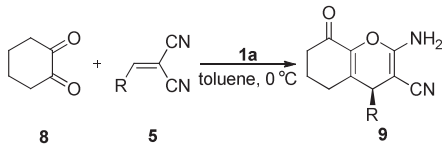
Entry	Solvent	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	toluene	**1a**	26	56	35
2	toluene	**1b**	30	41	35
3	toluene	**1c**	30	47	34
4	toluene	**1d**	28	37	30[d]
5	toluene	**1f**	28	61	16
6	toluene	**1h**	28	72	3[d]
7	toluene	**1m**	26	70	25[d]
8	toluene	**1i**	240	21	1[d]
9	toluene	**1j**	40	34	27[d]
10	toluene	**1n**	168	31	3
11	CH_2Cl_2	**1a**	30	43	18
12	Et_2O	**1a**	28	55	17
13	EtOAc	**1a**	28	35	25
14	THF	**1a**	40	33	33
15	$CHCl_3$	**1a**	38	33	6
16	CH_3CN	**1a**	28	31	15
17	EtOH	**1a**	28	53	40
18[e]	EtOH	**1a**	72	58	40
19[e]	toluene	**1a**	28	64	63
20[f]	toluene	**1a**	28	43	59

[a]Unless otherwise indicated, all reactions were conducted with benzylidenemalononitrile **5a** (0.30 mmol), cyclohexane-1,2-dione (**8**, 0.32 mmol), and the catalyst (0.030 mmol, 10 mmol %) in the specified solvent (1.5 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 as the major product in these cases.
[e]The reaction was conducted at 0°C.
[f]The reaction was conducted at −15°C.

As shown in Table 6, different cinchona alkaloid derivatives (**1a-d**, **1f**, **1h**, and **1m**) were screened using toluene as the solvent at room temperature (entries 1–7). All of these catalysts led to poor product ee values, with quinine thiourea (**1a**), dihydroquinine thiourea (**1b**), and cinchonidine thiourea (**1c**) yielding the highest product ee values (entries 1–3). Similarly, poor enantioselectivities were obtained with Takemoto thiourea catalysts **1i** and **1j** and a diamine catalyst **1n** (entries 8–10). On the basis of these results, quinine thiourea (**1a**) was chosen as the catalyst for further optimizations. Firstly, different organic solvents were screened (entries 11–17). As the data indicate, except for ethanol (entry 17), all the other solvents screened gave lower ee values as compared with that of

Table 7

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



8 **5** **9**

Entry	*R*	**5/9**	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	**a**	28	64	63
2	4-ClC_6H_4	**b**	24	60	58
3	4-BrC_6H_4	**c**	30	55	57
4	4-CNC_6H_4	**d**	24	51	43
5	4-$NO_2C_6H_4$	**e**	26	55	48
6	3-BrC_6H_4	**f**	24	63	52[d]
7	4-$CH_3C_6H_4$	**g**	28	49	50
8	thiophen-2-yl	**h**	30	37	47[e]
9	$CH_3(CH_2)_5$	**i**	96	12	9[d]

[a]All reactions were conducted with the benzylidenemalononitrile (**5**, 0.30 mmol), cyclohexane-1,2-dione (**8**, 0.32 mmol), and catalyst **1a** (0.030 mmol, 10 mol %) in toluene (1.5 mL) at 0°C. The product stereochemistry was tentatively assigned.
[b]Yield of isolated product after column chromatography.
[c]Unless otherwise specified, ee values were determined by HPLC analysis on a ChiralCel OD-H column.
[d]Determined by HPLC analysis on a ChiralPak AD-H column.
[e]Determined by HPLC analysis on a ChiralPak AS column.

toluene. Nonetheless, the attempt to increase the ee value of the reaction at lower temperatures using ethanol failed (entry 18). In contrast, the ee value of the product can be increased to 63% by conducting the reaction using toluene as the solvent at 0°C (entry 19). Further lowering the temperature to −15°C had detrimental effect both on reactivity and enantioselectivity of the reaction (entry 20).

Once the optimized reaction conditions were found, the other benzylidenemalononitriles were applied to this reaction under these conditions. The results are collected in Table 7. As shown in Table 7, benzylidenemalononitriles with various substituents all produce the desired product in mediocre to good ee values (43–63% ee, entries 1–7). The yields (49–64%) obtained are usually low because of the formation of some unidentified products in the reaction. The heterocyclic thiophen-2-ylmethylidenemalononitrile also gives the expected product in 47% ee and 37% yield (entry 8). However, the alkylidenemalononitrile **5i** reacts very slowly and leads to poor ee value of the product (entry 9).

Because products **9** were mostly viscous liquids, we were not able to obtain a suitable crystal for the X-ray crystallographic analysis. Thus, the absolute stereochemistry of the newly formed stereogenic center could not be determined in the same way as compounds **4** and **6**. Instead, the product stereochemistry was tentatively assigned as *S* because of the similarity of the mechanism of this reaction to those responsible for the formation of products **4** and **6** (Scheme 1).

CONCLUSION

In summary, we have realized the enantioselective synthesis of several 2-amino-4*H*-chromene derivatives using the cinchona alkaloid-derived bifunctional organocatalysts via the tandem Michael addition–cyclization reaction between 1,3-cyclohexanediones or 1,2-cyclohexanediones and (*E*)-3-aryl-2-cyanoacrylate or alkylidenemalononitrile derivatives. The optical purity of the products was found to be highly substrate-dependent and catalyst-dependent.

EXPERIMENTAL

All reactions were carried out in oven-dried glass wires. Solvents were dried using standard protocols. All chemicals and reagents were used as received. The catalysts were prepared according to the literature methods [14]. ^{1}H NMR (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz, respectively) spectra were recorded at 25°C using $CDCl_3$ or DMSO-d_6 as the solvent. Thin-layer chromatography (TLC) was performed with silica gel GF_{254} precoated on plastic plates, and spots were visualized with UV. HPLC analysis was performed on an HPLC instrument equipped with a ultraviolet–visible detector. High resolution mass spectrum (HRMS) was recorded using electrospray ionization technique with a time of flight analyzer. Elemental microanalysis was conducted by Atlantic Microlab Inc. (Norcross, GA 30071).

General procedure for the asymmetric synthesis of compound 4. A solution of 5,5-dimethylcyclohexane-1,3-dione (**2**, 35.3 mg, 0.10 mmol) and catalyst **1a** (5.9 mg. 0.010 mmol, 10 mol %) in toluene (1.0 mL) was stirred at 0°C for 15 min. To this solution was added alkyl (*E*)-2-cyano-3-phenylacrylate (**3**, 0.12 mmol), and the mixture was further stirred at 0°C until the reaction was completed (TLC monitoring). The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography (85:15 hexanes/EtOAc) to afford the product **4**.

(S)-Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4a). White solid, yield 31.3 mg (92%), mp: 160–161°C, $[\alpha]_D^{25}$ = +35.7 (c = 1.4, CH_2Cl_2, 79% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 1.02 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 3H), 2.08 (d, *J* = 16.2 Hz, 1H), 2.15 (d, *J* = 16.2 Hz, 1H), 2.35 (s, 2H), 3.92–3.99 (m, 2H), 4.62 (s, 1H), 6.10 (br. s, 2H), 7.02 (t, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 27.7, 29.3, 32.5, 34.1, 40.9, 51.0, 59.9, 81.1, 117.0, 126.3, 128.0, 128.5, 146.0, 158.5, 161.6, 169.4, 196.7 ppm. υ_{max} (neat, cm^{-1}): 3427, 3310, 2919, 1688, 1657, 1598, 1517, 1364, 1244. Anal. calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.39; H, 6.91; N, 4.07. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Methyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4b)[3b]. White solid, yield 29.4 mg (90%), mp: 149–150°C, $[\alpha]_D^{25}$ = +23.5 (c = 1.2, CH_2Cl_2, 69% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (s, 3H), 1.09 (s, 3H), 2.15 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.42 (s, 2H), 3.59 (s, 3H), 4.70 (s, 1H), 6.18 (br. s, 2H), 7.07–7.12 (m, 1H), 7.17–7.26 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 29.5, 32.6, 34.0, 41.0, 51.0, 51.3, 80.9, 117.1, 126.3, 128.1, 128.2, 145.8, 158.7, 161.5, 169.6, 196.4 ppm. υ_{max} (neat, cm^{-1}): 3389, 3296, 2952, 1688, 1651, 1530, 1437, 1364, 1244. Anal. calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.59; H, 6.48; N, 4.22. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4c). White solid, yield 30.1 mg (85%), mp: 161–162°C, $[\alpha]_D^{25}$ = +37.9 (c = 1.45, CH_2Cl_2, 80% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.2 Hz, 6H), 1.11 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 2.17 (d, J_1 = 16.3 Hz, 1H), 2.23(d, *J* = 16.3 Hz, 1H), 2.44 (s, 2H), 4.68 (s, 1H), 4.89 (septet, *J* = 6.2 Hz, 1H), 6.16 (br. s, 2H), 7.19–7.22 (m, 3H), 7.26–7.27 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.6, 27.8, 29.4, 32.6, 34.3, 41.0, 51.1, 67.2, 81.4, 116.9, 126.2, 127.8, 128.6, 146.0, 158.3, 161.5, 168.8, 196.6 ppm. υ_{max} (neat, cm^{-1}): 3447, 3320, 2958, 1686, 1665, 1596, 1367, 1241. Anal. calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.02; H, 7.01; N, 3.87. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4d). White solid, yield 32.8 mg (88%), mp: 127–128°C, $[\alpha]_D^{25}$ = +32.1 (c = 1.45, CH_2Cl_2, 74% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.2 Hz, 6H), 1.09 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 2.15 (d, *J* = 16.2 Hz, 1H), 2.23(d, *J* = 16.2 Hz, 1H), 2.41 (s, 2H), 4.64 (s, 1H), 4.88 (septet, *J* = 6.2 Hz, 1H), 6.18 (br. s, 2H), 6.83–6.89 (m, 2H), 7.18–7.22 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.6, 27.8, 29.4, 32.6, 33.7, 41.0, 51.0, 67.3, 81.1, 114.4, 114.7, 116.7, 130.0, 141.9, 158.2, 159.7, 161.5, 162.9, 168.7, 196.6 ppm. υ_{max} (neat, cm^{-1}): 3413, 3321, 2961, 1676, 1652, 1517, 1355, 1240, 1191, 1159. Anal. calcd. for $C_{21}H_{24}FNO_4$: C, 67.54; H, 6.48; N, 3.75. Found: C, 67.67; H, 6.44; N, 3.82. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4e). White solid, yield 33.0 mg (85%), mp: 142–144°C, $[\alpha]_D^{25}$ = +10.6 (c = 1.62, CH_2Cl_2, 76% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.0 Hz, 6H), 1.09 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 2.14 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.41 (s, 2H), 4.63 (s, 1H), 4.88 (septet, *J* = 6.0 Hz, 1H), 6.20 (br. s, 2H), 7.13–7.20 (m, 4*H*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 22.6, 27.8, 29.5, 32.6, 33.9, 41.0, 51.0, 67.3, 80.8, 116.46, 128.0, 130.0, 131.7, 144.7, 158.3, 161.6, 168.6, 196.6 ppm. υ_{max} (neat, cm^{-1}): 3411, 3316, 2965, 1675, 1656, 1517, 1335, 1238, 1191. Anal. calcd. for $C_{21}H_{24}ClNO_4$: C, 64.69; H, 6.20; N, 3.59. Found: C, 64.62; H, 6.34; N, 3.63. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4f). White solid, yield 39.4 mg (91%), mp: 162–163°C, $[\alpha]_D^{25}$ = +17.7 (c = 1.75, CH_2Cl_2, 75% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 7.9 Hz, 6H), 1.10 (s, 3H), 1.22 (d, *J* = 6.1 Hz, 3H), 2.16 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.42 (s, 2H), 4.63 (s, 1H), 4.89 (septet, *J* = 7.9 Hz, 1H), 6.21 (br. s, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 22.4, 27.6, 29.3, 32.5, 33.9, 40.9, 50.9, 67.3, 80.7, 116.4, 119.9, 130.4, 131.0, 145.3, 158.4, 161.7, 168.7, 196.7 ppm. υ_{max} (neat, cm^{-1}): 3399, 3291, 2930, 1686, 1657, 1613, 1519, 1363, 1248, 1191, 1161; Anal. calcd. for $C_{21}H_{24}BrNO_4$: C, 58.07; H, 5.57; N, 3.22. Found: C, 58.11; H, 5.64; N, 3.22. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4g). White solid, yield 28.5 mg (75%), mp: 153–154°C, $[\alpha]_D^{25}$ = -10.7 (c = 0.65, CH_2Cl_2, 66% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.2 Hz, 6H), 1.09 (s, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 2.14 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.43 (s, 2H), 4.69 (s, 1H), 4.86 (septet, *J* = 6.2 Hz, 1H), 6.26 (br. s, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.6, 27.7, 29.4, 32.6, 34.9, 41.0, 50.9, 67.4, 79.9, 109.9, 115.8, 119.4, 129.5, 131.8, 151.7, 158.4, 162.0, 168.3, 196.5 ppm; υ_{max} (neat, cm^{-1}): 3415, 3301, 2959, 2227, 1684, 1656, 1604, 1527, 1362, 1248, 1202. Anal. calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.30; H, 6.60; N, 7.18. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4h). White solid, yield 28.8 mg (72%), mp: 196–197°C, $[\alpha]_D^{25}$ = -1.8 (c = 1.1, CH_2Cl_2, 65% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 6.2 Hz, 6H), 1.10 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 2.14 (d, *J* = 16.3 Hz, 1H), 2.24 (d, *J* = 16.3 Hz, 1H), 2.44 (s, 2H), 4.75 (s, 1H), 4.87 (septet, *J* = 6.2 Hz, 1H), 6.28 (br. s, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 22.6, 27.7, 29.4, 32.6, 34.7, 41.0, 50.9, 67.5, 79.8, 115.7, 123.3, 129.5, 146.4, 153.8, 158.4, 162.2, 168.2, 196.5 ppm. υ_{max} (neat, cm^{-1}): 3462, 3331, 2959, 2187, 1686, 1659, 1625, 1508, 1371, 1250. Anal. calcd. for $C_{21}H_{24}N_2O_6$: C, 62.90; H, 6.04; N, 7.00. Found: C, 62.73; H, 5.94; N, 6.92; HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4i). White solid, yield 31.3 mg (85%), mp: 146–147°C, $[\alpha]_D^{25}$ = +9.0 (c = 1.3, CH_2Cl_2, 82% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98–1.03 (m, 6H), 1.09 (s, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 2.15 (d, *J* = 16.1 Hz, 1H), 2.22 (d, *J* = 16.1 Hz, 1H), 2.25 (s, 3H), 2.42 (s, 2H), 4.63 (s, 1H), 4.86 (septet, *J* = 6.2 Hz, 1H), 6.15 (br. s, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 22.1, 22.6, 27.9, 29.5, 32.6, 33.8, 41.0, 51.07, 67.2, 81.5, 117.0, 128.4, 128.6, 135.5, 143.1, 158.2, 161.5, 168.8, 196.7 ppm. υ_{max} (neat, cm^{-1}): 3407, 3302, 2958, 1686, 1657, 1613, 1511, 1364, 1283, 1199, 1161; Anal. calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.28; H, 7.23; N, 3.78. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4j). White solid, yield 32.3 mg (84%), mp: 127–128°C, $[\alpha]_D^{25}$ = +9.0 (c = 1.0, CH_2Cl_2, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 6.2 Hz, 6H), 1.10 (s, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 2.16 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.42 (s, 2H), 3.75 (s, 3H), 4.63 (s, 1H), 4.89 (septet, *J* = 6.2 Hz, 1H), 6.16 (br. s, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 22.5, 22.7, 29.3, 32.5, 33.3, 40.9, 51.0, 55.4, 67.1, 81.6, 113.3, 117.1, 129.5, 138.5, 158.0, 158.3, 161.4, 169.0, 196.9 ppm. υ_{max} (neat, cm^{-1}): 3407, 3304, 2958, 1686, 1655, 1607, 1508, 1364, 1243, 1199, 1161; Anal. calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.40; H, 7.03; N, 3.58. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4k). White solid, yield 39 mg (90%), mp: 180–182°C, $[\alpha]_D^{25}$ = −1.9 (c = 1.63, CH_2Cl_2, 74% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.3 Hz, 6H), 1.10 (s, 3H), 1.24 (d, *J* = 6.3 Hz, 3H), 2.18 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.44 (s, 2H), 4.63 (s, 1H), 4.9 (septet, *J* = 6.3 Hz, 1H), 6.23 (br. s, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.18–7.24 (m, 2H), 7.40 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 22.5, 27.7, 29.3, 32.5, 34.2, 40.9, 50.9, 67.3, 80.7, 116.2, 122.0, 127.3, 129.3, 129.5, 131.8, 148.5, 158.3, 161.9, 168.7, 195.6 ppm. υ_{max} (neat, cm^{-1}): 3405, 3293, 2944, 1686, 1654, 1620, 1519, 1359, 1248, 1199, 1159; Anal. calcd. for $C_{21}H_{24}BrNO_4$: C, 58.07; H, 5.57; N, 3.22. Found: C, 57.96; H, 5.59; N, 3.09. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(2-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4l). White solid, yield 36.8 mg (85%), mp: 172–174°C, $[\alpha]_D^{25}$ = +1.5 (c = 1.7, CH_2Cl_2, 20% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 6.3 Hz, 3H), 0.92 (s, 3H), 1.01 (s, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 2.05 (d, *J* = 16.1 Hz, 1H), 2.13 (d, *J* = 16.1 Hz, 1H), 2.33 (s, 2H), 4.78–4.88 (m, 1H), 4.89 (s, 1H), 6.20 (br. s, 2H), 6.83–6.88 (m, 1H), 7.04–7.09 (m, 1H), 7.19–7.21 (m, 1H), 7.31–7.34 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.5, 28.01, 29.3, 32.4, 35.5, 41.0, 51.1, 67.2, 79.9, 115.1, 123.9, 126.8, 127.7, 132.9, 133.3, 143.7, 158.6, 161.8, 168.9, 196.6 ppm. υ_{max} (neat, cm^{-1}): 3397, 3290, 2945, 1688, 1661, 1616, 1517, 1363, 1248, 1199, 1161. Anal. calcd. for $C_{21}H_{24}BrNO_4$: C, 58.07; H, 5.57; N, 3.22. Found: C, 58.28; H, 5.70; N, 3.26. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4m). White solid, yield 33.1 mg (86%), mp: 133–134°C, $[\alpha]_D^{25}$ = +10.3 (c = 1.55, CH_2Cl_2, 74% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.2 Hz, 6H), 1.09 (s, 3H), 1.24 (d, *J* = 6.2 Hz,

3H), 2.16 (d, *J* = 16.2 Hz, 1H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.41 (s, 2H), 3.76 (s, 3H), 4.65 (s, 1H), 4.88 (septet, *J* = 6.2 Hz, 1H), 6.18 (br. s, 2H), 6.61–6.65 (m, 1H), 6.81–6.85 (m, 2H), 7.09 (t, *J* = 7.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 22.6, 27.9, 29.4, 32.6, 34.3, 41.0, 51.1, 55.4, 67.2, 81.2, 111.4, 114.6, 116.8, 121.1, 128.7, 147.7, 158.3, 159.2, 161.5, 168.8, 196.6 ppm. υ_{max} (neat, cm^{-1}): 3405, 3304, 2961, 1686, 1655, 1508, 1357, 1243, 1191, 1161. Anal. calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.29; H, 7.07; N, 3.59. HPLC conditions: ChiralCel OD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.7 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-4-(2-methoxy-phenyl)-7,7-dimethyl-5-oxo--5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4n). White solid, yield 31.6 mg (82%), mp: 129–130°C, $[\alpha]_D^{25} = +9.0$ (c = 1.55, CH_2Cl_2, 51% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.2 Hz, 6H), 1.09 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 2.13 (d, *J* = 16.2 Hz, 1H), 2.21 (d, *J* = 16.2 Hz, 1H), 2.35 (d, *J* = 17.5 Hz, 1H), 2.43 (d, *J* = 17.5 Hz, 1H), 3.76 (s, 3H), 4.77 (s, 1H), 4.87 (septet, *J* = 6.2 Hz, 1H), 6.16 (br. s, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.82–6.85 (m, 1H), 7.08–7.12 (m, 1H), 7.33 (d, *J* = 7.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 22.5, 27.2, 29.6, 32.4, 41.0, 51.0, 55.4, 66.8, 79.5, 110.8, 114.8, 119.9, 127.6, 132.4, 158.0, 159.1, 162.3, 169.3, 196.9 ppm. υ_{max} (neat, cm^{-1}): 3407, 3317, 2965, 1686, 1655, 1617, 1505, 1364, 1244, 1199, 1161. Anal. calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.66; H, 7.03; N, 3.69. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-7,7-dimethyl-4-napthalen-1-yl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4o). White solid, yield 32.8 mg (81%), mp: 144–146°C, $[\alpha]_D^{25} = -2.3$ (c = 1.3, CH_2Cl_2, 65% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.30 (d, *J* = 6.2 Hz, 3H), 0.95 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 6H), 2.09 (d, *J* = 16.2 Hz, 1H), 2.19 (d, *J* = 16.2 Hz, 1H), 2.46 (s, 2H), 4.74 (septet, *J* = 6.2 Hz, 1H), 5.51 (s, 1H), 6.21 (br. s, 2H), 7.23–7.35 (m, 2H), 7.39–7.44 (m, 1H), 7.53–7.61 (m, 2H), 7.73–7.76 (m, 1H), 8.70–8.73 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 22.3, 27.9, 29.1, 29.4, 32.6, 41.1, 50.9, 66.9, 82.9, 117.8, 125.3, 125.4, 125,9, 126.5, 126.9, 128.2, 131.9, 133.4, 144.5, 158.2, 161.1, 169.0, 196.8 ppm. υ_{max} (neat, cm^{-1}): 3403, 3311, 2953, 1686, 1661, 1607, 1515, 1353, 1243. Anal. calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.06; H, 6.84; N, 3.39. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-7,7-dimethyl-5-oxo-4-thiophen-2-yl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4p). White solid, yield 24.1 mg (67%), mp: 156–157°C, $[\alpha]_D^{25} = +9.5$ (c = 0.6, CH_2Cl_2, 76% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.10 (d, *J* = 6.3 Hz, 6H), 1.25 (d, *J* = 6.2 Hz, 3H), 2.26 (s, 2H), 2.41 (s, 2H), 4.98 (septet, *J* = 6.3 Hz, 1H), 5.06 (s, 1H), 6.21 (br. s, 2H), 6.79–6.87 (m, 2H), 7.00–7.02 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 22.6, 27.9, 28.9, 29.5, 32.6, 41.0, 51.1, 67.4, 81.2, 116.6, 123.2, 124.3, 126.5, 150.7, 158.6, 162.0, 168.6, 196.5 ppm. υ_{max} (neat, cm^{-1}): 3415, 3304, 2965, 1687, 1650, 1612, 1278, 1370, 1277, 1198, 1164. Anal. calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.19; H, 6.32; N, 3.81. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

(S)-Isopropyl 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (4q). White solid, yield 27.1 mg (83%), mp: 122–124°C, $[\alpha]_D^{25} = +10.0$ (c = 0.6, CH_2Cl_2, 70% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.95–2.02 (m, 2H), 2.30–2.35 (m, 2H), 2.52–2.59 (m, 2H), 4.69 (s, 1H), 4.87 (septet, *J* = 6.2 Hz, 1H), 6.16 (br. s, 2H), 7.16–7.21 (m, 3H), 7.24–7.27 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 22.0, 22.6, 27.4, 34.2, 37.2, 67.2, 81.4, 118.2, 126.2, 127.9, 128.6, 146.2, 158.2, 163.1, 168.8, 196.7 ppm. υ_{max} (neat, cm^{-1}): 3443, 3317, 2965, 1686, 1659, 1596, 1347, 1241. Anal. calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.65; H, 6.63; N, 4.41. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 80:20, flow rate = 0.8 mL/min, UV detection at 254 nm.

General procedure for the asymmetric synthesis of compound 6. To a solution of 5,5-dimethylcyclohexane-1,3-dione (**2**, 11.2 mg, 0.10 mmol) and catalyst **1k** (0.60 mg, 0.0010 mmol, 1 mol %) in toluene (1.5 mL) at room temperature was added benzylidenemalononitrile (**5**, 0.12 mmol) in the present of. The mixture was further stirred at room temperature until completion (TLC monitoring). The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography (60:40 hexane/EtOAc) to afford the product **6**.

(R)-2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6a). White solid, yield 28.8 mg (98%), mp: 203–204°C, $[\alpha]_D^{25} = -10.8$ (c = 0.5, THF, 62% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.26 (t, *J* = 7.5 Hz, 2H), 7.20 – 7.09 (m, 3H), 6.97 (s, 2H), 4.15 (s, 1H), 2.54 (S, 2H), 2.23 (d, *J* = 16.2 Hz, 1H), 2.08 (d, *J* = 16.2 Hz, 2H), 1.02 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.0, 162.9, 158.9, 145.1, 128.7, 127.5, 127.0, 120.1, 113.1, 58.7, 50.4, 36.0, 32.2, 31.1, 28.8, 27.2 ppm. υ_{max} (neat, cm^{-1}): 3422, 2972, 2181, 1712, 1527, 1362. HRMS m/z calcd. for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1447; found 295.1441. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6b). White solid, yield 30 mg (96%), mp: 188–189°C, $[\alpha]_D^{25} = +6.2$ (c = 0.55,

THF, 54% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.22–7.05 (m, 5H), 7.03 (s, 2H), 4.18 (s, 1H), 2.52 (S, 2H), 2.23 (d, J = 16.1 Hz, 1H), 2.08 (d, J = 16.1 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.1, 162.9, 159.7, 158.8, 141.4, 141.3, 129.5, 129.4, 120.0, 115.6, 115.3, 113.01, 58.47, 50.3, 35.3, 32.2, 28.7, 27.2 ppm. υ_{max} (neat, cm^{-1}): 3415, 2982, 2205, 1751, 1422, 1303. HRMS m/z calcd. for $C_{18}H_{18}FN_2O_2$ $[M+H]^+$ 313.1352; found 313.1364. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6c). White solid, yield 31.5 mg (96%), mp: 205–206°C, $[\alpha]_D^{25} = -9.8$ (c = 0.8, THF, 53% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.06 (s, 2H), 4.17 (s, 1H), 2.46 (s, 2H), 2.23 (d, J = 16.1 Hz, 1H), 2.08 (d, J = 16.1 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.1, 163.0, 158.9, 144.2, 131.5, 129.5, 128.7, 120.0, 112.7, 58.1, 50.3, 35.5, 32.2, 28.7, 27.3 ppm. υ_{max} (neat, cm^{-1}): 3396, 2966, 2182, 1606, 1386. HRMS m/z calcd. for $C_{18}H_{18}ClN_2O_2$ $[M+H]^+$ 329.1057; found 329.1074. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6d). White solid, yield 36.5 mg (98%), mp: 199–200°C, $[\alpha]_D^{25} = -14.1$ (c = 0.7, THF, 54% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.45 (d, J = 8.3 Hz, 2H), 7.07–7.11 (m, 4H), 4.15 (s, 1H), 2.48 (s, 2H), 2.23 (d, J = 16.0 Hz, 1H), 2.07 (d, J = 16.0 Hz, 1H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ δ 196.1, 163.0, 158.9, 144.6, 131.6, 129.9, 120.0, 112.6, 58.0, 55.3, 50.3, 35.6, 32.2, 28.7, 27.3. υ_{max} (neat, cm^{-1}): 3423, 2968, 2180, 1723, 1414, 1201. HRMS m/z calcd. for $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ 373.0552; found 373.0554. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6e). White solid, yield 29.3 mg (92%), mp: 186–187°C, $[\alpha]_D^{25} = +13.2$ (c = 0.7, THF, 31% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.90–7.62 (m, 2H), 7.53–7.25 (m, 2H), 7.14 (s, 2H), 4.27 (s, 1H), 2.51 (s, 2H), 2.24 (d, J = 16.0 Hz, 1H), 2.09 (d, J = 16.0 Hz, 1H), 1.02 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ196.1, 163.5, 158.9, 150.6, 132.8, 128.7, 119.8, 119.2, 112.1, 109.8, 57.5, 50.3, 36.2, 32.2, 28.6, 27.4 ppm. υ_{max} (neat, cm^{-1}): 3441, 2981, 2210, 1682, 1381, 1166. HRMS m/z calcd. for $C_{18}H_{18}N_3O_2$ $[M+H]^+$ 320.1399; found 320.1390. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6f). White solid, yield 31.8 mg (94%), mp: 182–183°C, $[\alpha]_D^{25} = +31.2$ (c = 0.5, THF, 36% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.15 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.15 (s, 2H), 4.34 (s, 1H), 2.52 (s, 2H), 2.24 (d, J = 16.1 Hz, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.1, 163.5, 159.0, 152.7, 146.6, 129.0, 124.1, 119.8, 112.1, 57.3, 50.2, 36.0, 32.2, 28.7, 27.3 ppm. υ_{max} (neat, cm^{-1}): 3488, 2972, 2185, 1740, 1256, 1122. HRMS m/z calcd. for $C_{18}H_{18}N_3O_4$ $[M+H]^+$ 340.1297; found 340.1304. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6g). White solid, yield 28.03 mg (91%), mp: 215–216°C, $[\alpha]_D^{25} = +37.8$ (c = 1.0, THF, 64% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.06 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 6.93 (s, 2H), 4.10 (s, 1H), 2.53 (s, 2H), 2.28–2.17 (m, 3H), 2.07 (d, J = 16.0 Hz, 1H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.0, 162.7, 158.8, 142.2, 136.0, 129.3, 127.5, 120.1, 113.3, 58.8, 50.4, 35.6, 32.2, 28.8, 27.2, 21.0 ppm. υ_{max} (neat, cm^{-1}): 3502, 2956, 2189, 1705, 1192. HRMS m/z calcd. for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1603; found 309.1611. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6h). White solid, yield 23.9 mg (74%), mp: 206–207°C, $[\alpha]_D^{25} = -21.1$ (c = 0.6, THF, 60% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ7.07–6.99 (m, 2H), 6.95 (s, 2H), 6.90–6.77 (m, 2H), 4.09 (s, 1H), 3.69 (s, 3H), 2.58 (s, 2H), 2.23 (d, J = 16.2 Hz, 1H), 2.06 (d, J = 16.2 Hz, 1H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.1, 162.5, 158.8, 158.3, 137.2, 128.6, 120.2, 114.0, 113.4, 58.9, 55.4, 55.3, 51.0, 50.4, 44.6, 35.1, 32.2, 28.8, 27.2 ppm. υ_{max} (neat, cm^{-1}): 3463, 2988, 2192, 1755, 1282. HRMS m/z calcd. for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1552; found 325.1563. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6i). White solid, yield 34.7 mg (93%), mp: 216–217°C, $[\alpha]_D^{25} = +13.2$ (c = 0.9, THF, 19% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.42 (d, J = 8.0 Hz, 1H), 7.36–7.24 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.14 (s, 2H), 4.22 (s, 1H), 2.55 (s, 2H), 2.28 (d, J = 16.1 Hz, 1H), 2.14 (d, J = 16.1 Hz, 1H), 1.06 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.2, 163.3, 158.9, 147.9, 131.1, 130.4, 130.0, 126.8, 122.0, 120.0, 112.5, 58.0, 50.3, 35.8, 32.3, 28.8, 27.2 ppm. υ_{max} (neat, cm^{-1}): 3425, 2898, 2202, 1652,

1313. HRMS m/z calcd. for $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ 373.0552; found 373.0559. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(2-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6j). White solid, yield 35.4 mg (95%), mp: 208–210°C, $[\alpha]_D^{25} = +17.2$ (c = 1, THF, 51% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.50 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 15.1, 7.5 Hz, 2H), 7.00 (s, 2H), 4.69 (s, 1H), 2.50 (s, 2H), 2.22 (d, *J* = 16.0 Hz, 1H), 2.05 (d, *J* = 16.0 Hz, 1H), 1.02 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 195.9, 163.4, 158.9, 143.8, 133.0, 130.2, 128.8, 128.5, 123.1, 119.5, 112.5, 57.4, 50.3, 35.4, 32.2, 28.8, 27.4 ppm. υ_{max} (neat, cm^{-1}): 3499, 2878, 2184, 1702, 1265. HRMS m/z calcd. for $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ 373.0552; found 373.0553. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6k). White solid, yield 27.88 mg (86%), mp: 194–195°C, $[\alpha]_D^{25} = -7.5$ (c = 0.65, THF, 45% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (t, *J* = 7.8 Hz, 1H), 6.99 (s, 2H), 6.72 (dd, *J* = 16.6, 7.8 Hz, 2H), 6.63 (s, 1H), 4.12 (s, 1H), 3.69 (s, 3H), 2.50 (s, 2H), 2.24 (d, *J* = 16.0 Hz, 1H), 2.09 (d, *J* = 16.0 Hz, 1H), 1.02 (s, 3H), 0.95 (s, 3H) ; ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.0, 163.0, 159.6, 158.9, 146.7, 129.8, 120.1, 119.7, 113.6, 113.0, 111.8, 58.6, 55.35, 50.3, 35.8, 32.2, 28.8, 27.1 ppm. υ_{max} (neat, cm^{-1}): 3515, 2902, 2190, 1764, 1293. HRMS m/z calcd. for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1552; found 325.1560. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-4-(2-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6l). White solid, yield 26.5 mg (82%), mp: 201–202°C, $[\alpha]_D^{25} = +14.2$ (c = 0.8, THF, 51% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.17–7.10 (m, 1H), 6.99–6.89 (m, 2H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.80 (s, 2H), 4.45 (s, 1H), 3.72 (s, 3H), 2.52 – 2.46 (s, 2H), 2.22 (d, *J* = 16.1 Hz, 1H), 2.04 (d, *J* = 16.1 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 196.0, 163.5, 159.4, 157.2, 132.5, 128.9, 128.2, 120.7, 120.2, 112.3, 111.9, 67.9, 57.8, 56.0, 55.3, 51.0, 50.4, 44.8, 32.2, 30.7, 29.0, 26.9 ppm. υ_{max} (neat, cm^{-1}): 3466, 2912, 2178, 1644, 1113. HRMS m/z calcd. for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1552; found 325.1569. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-7,7-dimethyl-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6m). White solid, yield 18.9 mg (63%), mp: 181–182°C, $[\alpha]_D^{25} = +37.6$ (c = 0.6, THF, 52% ee). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.29 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.09 (s, 2H), 6.88 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.84 (d, *J* = 2.9 Hz, 1H), 2.51 (t, *J* = 14.7 Hz, 1H), 2.41 (d, *J* = 17.7 Hz, 1H), 2.28 (d, *J* = 16.2 Hz, 1H), 2.13 (d, *J* = 16.1 Hz, 1H), 1.02 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.9, 162.9, 159.3, 149.7, 127.2, 124.8, 124.4, 120.0, 113.3, 58.5, 50.3, 32.1, 30.8, 29.0, 26.9 ppm. υ_{max} (neat, cm^{-1}): 3505, 2992, 2188, 1724, 1363. HRMS m/z calcd. for $C_{16}H_{14}N_2O_2S$ $[M+H]^+$ 301.1011; found 301.1013. HPLC conditions: ChiralPak IB, hexanes/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, UV detection at 254 nm.

(R)-2-Amino-5,6,7,8-tetrahydro-5-oxo-4-phenyl-4H-chromene-3-carbonitrile (6n). White solid, yield 19.4 mg (73%), mp: 210–211°C, $[\alpha]_D^{25} = +23.8$ (c = 0.6, THF, 52% ee). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.26 (t, *J* = 7.2 Hz, 2H), 7.12–7.18 (m, 3H), 6.97 (s, 2H), 4.17 (s, 1H), 2.61 (s, 2H), 2.25–2.27 (m, 2H), 2.05–1.74 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.3, 165.2, 159.0, 144.4, 131.7, 129.7, 128.9, 120.2, 114.0, 58.4, 37.1, 35.8, 27.3, 20.6 ppm. υ_{max} (neat, cm^{-1}): 3485, 2964, 2186, 1702, 1322. HRMS m/z calcd. for $C_{16}H_{15}N_2O_2$ $[M+H]^+$ 267.1134; found 273.1140. HPLC conditions: ChiralPak AD-H, hexanes/*i*-PrOH = 85:15, flow rate = 1.0 mL/min, UV detection at 254 nm.

General procedure for the asymmetric synthesis of compound 9. To a solution of cyclohexane-1,2-dione (**8**, 35.3 mg, 0.32 mmol) and catalyst **1a** (17.8 mg, 0.030 mmol, 10 mol %) in toluene (1.5 mL) at 0°C was added benzylidenemalononitrile (**5**, 0.30 mmol). The mixture was stirred until the reaction was completed (TLC monitoring). The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography (5:1 hexane/EtOAc) to afford the product **9**.

(S)-2-Amino-8-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9a). Viscous oil, yield 51.1 mg (64%), $[\alpha]_D^{25} = +30.0$ (c 0.395, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.38 (m, 3H), 7.22–7.23 (m, 2H), 4.74 (s, 2H), 4.10 (s, 1H), 2.45–2.58 (m, 2H), 2.12–2.27 (m, 2H),1.86–2.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 159.0, 141.5, 140.5, 134.8, 129.4, 128.3, 128.2, 119.3, 59.5, 44.0, 38.0, 27.7, 21.9; ν_{max} (cm^{-1}): 3322, 2923, 2190, 1596; Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.22; H, 5.15; N, 10.51; HPLC conditions: ChiralCel OD-H column, 15:85 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(4-chlorophenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9b). Viscous oil, yield 54.1 mg (60%), $[\alpha]_D^{25} = -25.2$ (c = 0.72, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.86 (s, 2H), 4.10 (s, 1H), 2.49–2.56 (m, 2H), 2.09–2.25 (m, 2H), 1.88–2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ190.6, 159.2, 140.5, 140.0, 134.2, 134.1, 129.6, 129.6, 119.2, 58.9, 43.4, 38.0, 27.6, 21.9; ν_{max} (cm^{-1}): 3436, 3322, 2190,

1668; Anal. calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.65; H, 4.36; N, 9.30; HPLC conditions: ChiralCel OD-H column, 15:85 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(4-bromophenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9c). Viscous oil, yield 56.9 mg (55%), $[\alpha]_D^{25} = -63.8$ (c 0.515, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 4.76 (s, 2H), 4.09 (s, 1H), 2.49–2.56 (m, 2H), 2.20–2.25 (m, 1H),2.10–2.16 (m 1H), 1.88–2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 159.0, 140.5, 140.4, 133.9, 132.5, 129.8, 122.4, 119.0, 59.1, 43.6, 38.1, 27.8, 22.0; ν_{max} (cm^{-1}): 2922, 2192, 1632; HRMS m/z calcd. for $C_{16}H_{14}BrN_2O_2$ $[M+H]^+$ 345.0233; found 345.0218; HPLC conditions: ChiralCel OD-H column, 15:85 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(4-cyanophenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9d). Pale yellow solid, yield 44.5 mg (51%), mp: 101–103°C, $[\alpha]_D^{25} = -40.7$ (c 0.685, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 4.91 (s, 2H), 4.19 (s, 1H), 2.45–2.57 (m, 2H), 2.22–2.28 (m, 1H), 1.90–2.11 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 159.3, 146.6, 140.9, 133.3, 132.8, 129.0, 118.8, 118.6, 112.4, 58.2, 44.1, 37.9, 27.7, 21.8; ν_{max} (cm^{-1}): 3517, 2231, 1766, 1609; HRMS m/z calcd. for $C_{17}H_{14}N_3O_2$ $[M+H]^+$ 292.1081; found 292.1077; HPLC conditions: ChiralCel OD-H column, 30:70 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(4-nitrophenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9e). Pale yellow solid, yield 51.3 mg (55%), mp: 203–205°C (decompose), $[\alpha]_D^{25} = -19.1$ (c 0.87, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 4.90 (s, 2H), 4.27 (s, 1H), 2.48–2.60 (m, 2H), 2.25–2.31(m, 1H), 1.91–2.12(m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ190.2, 159.3, 148.5, 148.0, 140.9, 132.6, 132.6, 129.2, 124.7, 118.7, 58.2, 43.8, 37.9, 27.7, 21.8; ν_{max} (cm^{-1}): 3427, 2921, 2190; Anal. calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.69; H, 4.02; N, 13.25; HPLC conditions: ChiralCel OD-H column, 40:60 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(3-bromophenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9f). Viscous oil, yield 65.1 mg (63%), $[\alpha]_D^{25} = -46.3$ (c 0.885, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.46 (m, 1H), 7.21–7.26 (m, 2H), 7.15–7.18 (m, 1H), 4.82 (s, 2H), 4.08 (s, 1H), 2.50–2.57 (m, 2H), 2.09–2.28 (m, 2H), 1.89–2.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 159.1, 143.7, 140.5, 133.8, 131.6, 131.1, 130.9, 126.9, 123.5, 119.0, 58.9, 43.9, 38.1, 27.8, 22.0; ν_{max} (cm^{-1}): 3435, 2184, 1692; HRMS m/z calcd. for $C_{16}H_{14}BrN_2O_2$ $[M+H]^+$ 345.0233; found 345.0226; HPLC conditions: ChiralPak AD-H column, 30:70 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-(4-methylphenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9g). Viscous liquid, yield 41.2 mg (49%), $[\alpha]_D^{25} = -72.9$ (c 0.305, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, $J = 7.8$ Hz, 2H), 7.09 (d, $J = 7.8$ Hz, 2H), 4.71 (s, 2H), 4.06 (s, 1H), 2.48–2.55 (m, 2H), 2.35 (s, 3H), 2.17–2.23 (m, 2H), 1.86–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.6, 158.8, 140.4, 138.4, 138.0, 135.0, 130.0, 128.0, 59.7, 43.7, 38.2, 27.9, 22.1, 21.5; ν_{max} (cm^{-1}): 3353, 3189, 2203, 1601; HRMS m/z calcd. for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1285; found 281.1292; HPLC conditions: ChiralCel OD-H column, 15:85 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-8-oxo-4-(thiophenyl-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9h). Viscous liquid, yield 30.1 mg (37%), $[\alpha]_D^{25} = -24.1$ (c 0.02, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.29 (m, 1H), 6.96–6.98 (m, 2H), 4.80 (s, 2H), 4.44 (s, 1H), 2.48–2.55 (m, 2H), 2.27–2.38 (m, 2H), 1.94–2.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 159.0, 145.6, 140.1, 133.9, 127.3, 126.2, 126.2, 119.0, 59.6, 38.9, 38.0, 27.7, 22.0; ν_{max} (cm^{-1}): 3403, 2963, 2203, 1601; HRMS m/z calcd. for $C_{14}H_{13}N_2O_2S$ $[M+H]^+$ 273.0692; found 273.0690; HPLC conditions: ChiralPak AS column, 65:35 *i*-PrOH/hexane, flow rate 1.0 mL/min, UV detection at 254 nm.

(S)-2-Amino-4-hexyl-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9i). Viscous liquid, yield 9.8 mg (12%), $[\alpha]_D^{25} = -6.5$ (c 0.03, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 (s, 2H), 3.14–3.16 (m, 1H), 2.47–2.59 (m, 3H), 2.23–2.29 (m, 1H), 2.01–2.06 (m, 2H), 1.57–1.71 (m, 3H), 1.16–1.38 (m, 7H), 0.87–0.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 160.4, 141.8, 136.2, 119.8, 57.2, 38.0, 37.2, 33.5, 31.9, 29.5, 27.6, 24.8, 22.8, 22.1, 14.3; ν_{max} (cm^{-1}): 3331, 2186, 1664; Anal. calcd for $C_{16}H_{13}N_3O_4$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 7.94; N, 10.22; HPLC conditions: ChiralPak AD-H column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, UV detection at 254 nm.

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[16] During the progress of our research, Du *et al*. reported a similar study of this reaction, see ref. 7a.

[17] CCDC 903532 contains the supplementary crystallographic data for compound **6a**. These data can be obtained free of charge from the Cambridge Crystallographic Data center via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx

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