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Organocatalytic Asymmetric Michael Addition of 1,3-Cyclohexanedione to Benzylidenemalonitriles

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The organocatalytic enantioselective Michael addition reaction promoted by chiral binaphthyl-modified squaramide catalyst have been developed, allowing facile synthesis of the corresponding chiral 2-amino-4*H*-chromenes derivatives with excellent enantioselectivity (up to 99% ee). The method reported represents a practical entry for the preparation of chiral 2-amino-4*H*-chromenes derivatives.

Key Words : Asymmetric catalysis, Organocatalysis, Michael addition, 2-Amino-4*H*-chromenes

Introduction

The chromene core is present as a characteristic structural motif in a large number of natural products and biologically active molecules.[1] Among the different type of chromene derivatives, 2-amino-4*H*-chromenes and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals.[2] The Michael reaction is widely recognized as one of the most fascinating and powerful methods for the formation of C-C bonds in organic synthesis[3] and the development of asymmetric version of this reaction has been the subject of intensive research.[4] Enantioselective organocatalytic Michael addition of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds represents a direct approach to chiral 1,5-dicarbonyl compounds that are versatile intermediates in organic synthesis.[5] Compared with α,β-unsaturated carbonyl compounds, reactions with benzylidenemalonitriles as Michael acceptors are limited. Very recently, cinchona- or rosin-derived thiourea-catalyzed Michael additions of cyclic 1,3-dicarbonyl compounds to benzylidenemalonitriles were applied to the synthesis of optically active 2-amino-4*H*-chromene derivatives.[6] There are still some drawbacks in the previously reported procedures, such as high catalyst loading and enantioselectivity. Accordingly, the development of alternative catalysts for enantioselective Michael addition of cyclic 1,3-dicarbonyl compounds to benzylidenemalonitriles is desirable.

Results and Discussion

As part of our research program related to the development

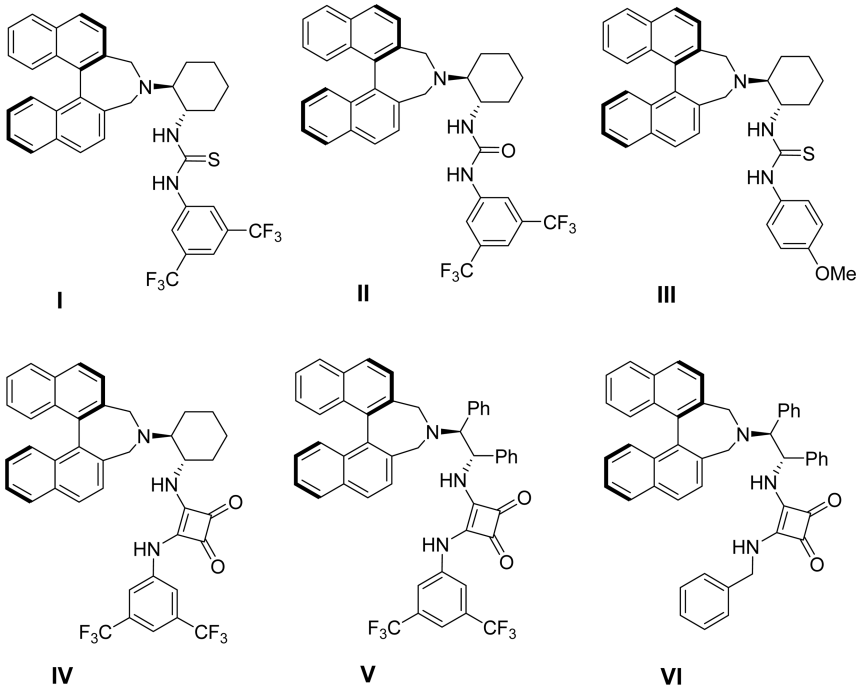
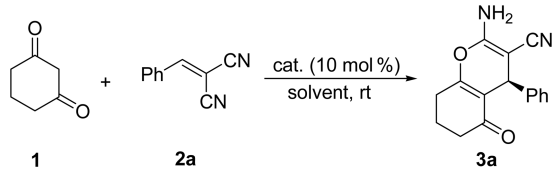


Figure 1. Structure of chiral bifunctional organocatalysts.

of synthetic methods for the enantioselective construction of stereogenic carbon centers,[7] we recently reported the asymmetric Michael addition of 1,3-dicarbonyl compounds using chiral catalysts.[8] Herein, we wish to describe the enantioselective synthesis of 2-amino-4*H*-chromenes *via* Michael addition/cyclization sequence of 1,3-cyclohexanedione to benzylidenemalonitriles promoted by binaphthyl-modified organocatalysts.

To determine suitable reaction conditions for the catalytic enantioselective Michael addition of 1,3-cyclohexanedione, we initially investigated a reaction system with 1,3-cyclohexanedione (**1**) and 2-benzylidenemalonitrile (**2a**) in the presence of 10 mol% binaphthyl-modified organocatalysts **I-VI** (Figure 1) bearing both central and axial chiral elements. As shown in Table 1, binaphthyl-modified (thio)urea catalysts **I-III** effectively promoted the reaction in toluene with moderate enantioselectivities (entries 1-3, Table 1). Change to the urea-moiety to squaramide organocatalysts **IV-VI** improved enantioselectivities (entries 4-6, Table 1), and the highest enantiselectivities obtained with the binaphthyl-modified squaramide catalyst **IV**. In order to further improve the selectivity, different solvents were then tested in the presence of 10 mol % of catalyst **IV**. Aprotic solvents

Table 1. Optimization of the reaction conditions [a]

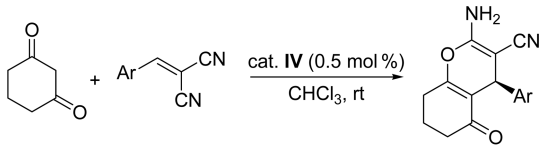


1 **2a** **3a**

Entry	Cat.	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	**I**	PhMe	7	95	29
2	**II**	PhMe	7	94	61
3	**III**	PhMe	7	93	75
4	**IV**	PhMe	4	93	97
5	**V**	PhMe	4	89	93
6	**VI**	PhMe	7	91	76
7	**IV**	*p*-xylene	4	38	75
8	**IV**	mesitylene	4	97	77
9	**IV**	Et_2O	10	71	98
10	**IV**	CH_2Cl_2	2	86	98
11	**IV**	$CHCl_3$	2	92	99
12	**IV**	DCE	2	78	97
13	**IV**	THF	12	74	96
14	**IV**	EtOH	2	77	4
15	**IV**	DMSO	2	69	5
16[d]	**IV**	$CHCl_3$	4	85	99
17[e]	**IV**	$CHCl_3$	6	91	99
18[f]	**IV**	$CHCl_3$	6	92	99
19[g]	**IV**	$CHCl_3$	6	92	99
20[h]	**IV**	$CHCl_3$	24	66	97

[a]Reaction conditions: 1,3-cyclohexanedione (**1**, 0.2 mmol), benzylidenemalonitriles **2a** (0.2 mmol), catalyst (0.02 mmol), solvent (0.6 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using a Chiralcel OD-H column. [d]5 mol % catalyst loading. [e]2.5 mol % catalyst loading. [f]1.0 mol % catalyst loading. [g]0.5 mol % catalyst loading. [h]0.25 mol % catalyst loading.

Table 2. Enantioselective synthesis of 2-amino-4*H*-chromene derivatives **3**[a]



1 **2** **3**

Entry	**2**, Ar	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	6	**3a**, 92	99
2	4-MeO-C_6H_4	26	**3b**, 77	98
3	4-Me-C_6H_4	9	**3c**, 91	98
4	4-Cl-C_6H_4	12	**3d**, 77	98
5	4-Br-C_6H_4	7	**3e**, 78	97
6	4-F-C_6H_4	6	**3f**, 91	98
7	4-CN-C_6H_4	8	**3g**, 88	99
8	4-NO_2-C_6H_4	6	**3h**, 84	97
9	3-MeO-C_6H_4	6	**3i**, 74	95
10	2-F-C_6H_4	6	**3j**, 97	96
11	2-thienyl	18	**3k**, 96	96
12	2-naphthyl	6	**3l**, 97	92

[a]Reaction conditions: 1,3-cyclohexanedione (**1**, 0.4 mmol), benzylidenemalonitriles **2** (0.4 mmol), catalyst (2.0 μmol), $CHCl_3$ (1.2 mL) at room temperature. [b]Isolated yield. [c]Enantiopurity was determined by HPLC analysis using a Chiralcel OD-H column.

such as toluene, *p*-xylene, mesitylene, diethyl ether, dichloromethane, chloroform, 1,2-dichloroethane, and THF were well tolerated in this Michael addition without a significant decrease of enantioselectivities (75-99% ee, entries 4 and 7-13, Table 1). However, protic solvent such as EtOH and dimethyl sulfoxide afforded products with low selectivities (entries 14-15, Table 1). Among the solvents probed, the best result was achieved when the reaction was conducted in chloroform (92% yield, 99% ee, entry 11, Table 1). The present catalytic system tolerates catalyst loading down to 5, 2.5, 1.0, or 0.5 mol %, and both the yields and enantioselectivities were retained (entries 4 and 16-20, Table 1).

With the optimal reaction conditions in hand, the asymmetric Michael additions of 1,3-cyclohexanedione to various benzylidenemalonitriles were examined, and the results are summarized in Table 2. As demonstrated, the organocatalyst **IV** catalyzed the Michael addition of 1,3-cyclohexanedione

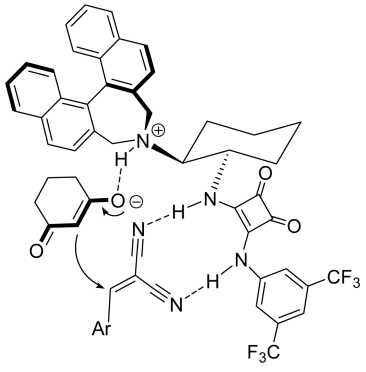
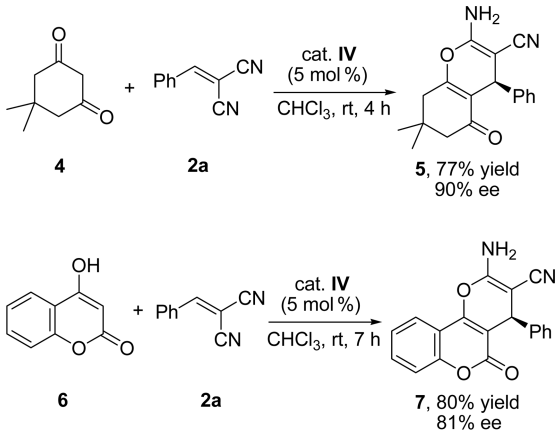
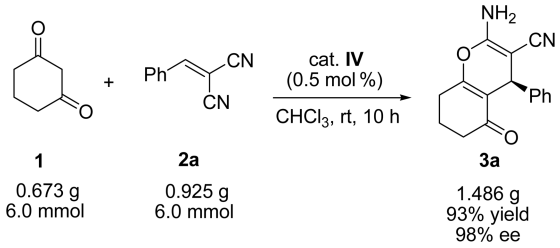


Figure 2. Proposed stereochemical model.



Scheme 1. The asymmetric Michael addition of 5,5-dimethyl-1,3-cyclohexanedione (**4**) and 4-hydroxycoumarin (**6**) with benzylidenemalononitrile (**2a**).



Scheme 2. Gram scale asymmetric synthesis of 2-amino-4*H*-chromene derivatives **3a**.

(**1**) to benzylidenemalonitriles **2** providing a general method for the synthesis of optically active 2-amino-4*H*-chromenes derivatives **3** with high to excellent enantiomeric excess (up to 99% ee). Absolute configuration of products were determined by comparison either of the optical rotation or chiral HPLC data with those of the reported ones.[6]

Although the reason for the observed enantioselectivity is still unclear, we believe that a carbonyl group of the benzylidenemalononitrile is activated by the squaramide moiety through hydrogen bonding, and the 1,3-cyclohexanedione moiety is activated by the basic nitrogen atom in tertiary amine (Figure 2). These interactions control the stereochemical outcome of the reaction and increase the reaction rate.

In addition, we investigated the asymmetric Michael addition-cyclization of 5,5-dimethyl-1,3-cyclohexanedione (**4**) and 4-hydroxycoumarin (**6**) to benzylidenemalononitrile (**2a**) under the similar conditions. The results are listed in Scheme 1. Comparable high yields and high enantioselectivities were obtained in these two cases.

The present method is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As shown in Scheme 2, when 1,3-cyclohexanedione (**1**) was treated with benzylidenemalonitriles **2a** under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired (*R*)-2-amino-5,6,7,8-tetrahydro-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (**3a**) at the gram scale with 93% yield and 98% ee (Scheme 2).

Conclusion

We have developed a binaphthyl-modified squaramide-catalyzed highly enantioselective Michael addition of 1,3-cyclohexanedione (**1**) to benzylidenemalonitriles **2** to afford biologically valuable 2-amino-4*H*-chromene derivatives **3**. This catalytic reaction at a low catalyst loading (0.5 mol %) was effective to give the Michael/cyclization adducts with high yields and excellent enantioselectivities (up to 99% ee) under mild reaction conditions. Further studies on asymmetric reactions catalyzed by binaphthyl-modified squaramides are underway in our laboratory.

Experimental

All commercial reagents and solvents were used without purification. TLC analyses were carried out on pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm), I_2, *p*-anisaldehyde, ninhydrin, and phosphomolybdic acid solution as an indicator. Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shift values (δ) are reported in ppm relative to Me_4Si (0.0 ppm). Optical rotations were measured on a JASCO-DIP-1000 digital polarimeter with a sodium lamp. The enantiomeric excesses (ee's) were determined by HPLC. HPLC analysis was performed on Younglin M930 Series and Younglin M720 Series, measured at 254 nm using the indicated chiral column.

General Procedure for the Michael Addition of 1,3-Dicarbonyl Compounds to Benzylidenemalonitriles 2. To a stirred solution of benzylidenemalonitriles **2** (0.4 mmol) and binaphthyl-modified squaramide **IV** (1.4 mg, 2.0 μmol) in chloroform (1.2 mL) was added 1,3-dicarbonyl compounds (0.4 mmol) at room temperature. The reaction mixture was stirred at room temperature for a specified period of reaction time (Table 2). The reaction mixture was purified by column chromatography (EtOAc/1,2-dichloroethane = 1:25) to give the desired product **3**.

(*R*)-2-amino-5,6,7,8-tetrahydro-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (3a): $[\alpha]_D^{25}$ = +22.0 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (t, *J* = 7.4 Hz, 2H), 7.14-7.20 (m, 3H), 7.00 (s, 2H), 4.18 (s, 1H), 2.59-2.62 (m, 2H), 2.22-2.32 (m, 2H), 1.87-1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 164.6, 158.5, 144.8, 128.4, 127.2, 126.6, 119.9, 113.8, 58.2, 36.4, 35.5, 26.5, 19.9; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 11.27 min (minor), 12.37 min (major), 99% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile (3b): $[\alpha]_D^{26}$ = +22.8 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.96 (s, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.13 (s, 1H), 2.50-2.60 (m, 2H), 2.21-2.32 (m, 2H), 1.83-1.98 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.9, 164.2, 158.4,

157.9, 136.9, 128.2, 119.9, 114.1, 113.7, 58.4, 55.0, 36.4, 34.6, 26.5, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 12.95 min (minor), 17.70 min (major), 98% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-5-oxo-4-*p*-tolyl-4*H*-chromene-3-carbonitrile (3c): $[\alpha]_D^{26}$ = +23.7 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.08 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.95 (s, 2H), 4.13 (s, 1H), 2.50-2.60 (m, 2H), 2.20-2.30 (m, 2H), 1.85-1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.9, 164.3, 158.5, 141.9, 135.6, 128.9, 127.1, 119.8, 114.0, 58.3, 36.4, 35.0, 26.5, 20.6, 19.9; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 8.5 min (minor), 9.9 min (major), 98% ee.

(*R*)-2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (3d): $[\alpha]_D^{24}$ = 10.2 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 2H), 4.29 (s, 1H), 2.60-2.62 (m, 2H), 2.24-2.31 (m, 2H), 1.90-1.98 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 165.2, 158.6, 150.3, 132.5, 128.4, 119.5, 118.9, 112.8, 57.1, 36.3, 35.7, 26.5, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 16.3 min (minor), 18.8 min (major), 98% ee.

(*R*)-2-amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (3e): $[\alpha]_D^{26}$ = +34.0 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, *J* = 13.6 Hz, 2H), 7.11-7.14 (d, *J* = 13.6, 2H), 7.07 (s, 2H), 4.18 (s, 1H), 2.61-2.62 (m, 2H), 2.22-2.31 (m, 2H), 1.88-1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 164.6, 158.4, 144.3, 131.4, 129.7, 119.8, 117.4, 113.5, 57.7, 36.6, 35.3, 26.7, 20.0; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 8.7 min (minor), 10.2 min (major), 97% ee.

(*R*)-2-amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (3f): $[\alpha]_D^{26}$ = +16.8 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18-7.21 (m, 2H), 7.07-7.12 (t, *J* = 8.8 Hz, 2H), 7.01 (s, 2H), 4.20 (s, 1H), 2.50-2.61 (m, 2H), 2.25-2.31 (m, 2H), 1.88-1.97 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 164.6, 162.2, 159.7, 158.5, 141.0 (d, *J* = 3.0 Hz), 129.1 (d, *J* = 7.6 Hz), 119.7, 115.2 (d, *J* = 84.0 Hz), 113.7, 58.1, 36.3, 34.8, 26.5, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 9.9 min (minor), 11.1 min (major), 98% ee.

(*R*)-2-amino-4-(4-cyanophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (3g): $[\alpha]_D^{25}$ = +19.6 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8 Hz, 2H), 7.15 (s, 2H), 4.29 (s, 1H), 2.50-2.63 (m, 2H), 2.25-2.32 (m, 2H), 1.94-1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 165.2, 158.6, 150.3, 132.5, 128.4, 119.5, 118.9, 112.8, 57.1, 36.3, 35.7, 26.5, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 9.9 min (minor), 11.1 min (major), 99% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-4-(4-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile (3h): $[\alpha]_D^{25}$ = +10.2 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.18 (s, 2H), 4.36 (s, 1H), 2.62-2.65 (m, 2H), 2.23-2.35 (m, 2H), 1.90-2.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 165.2, 158.7, 152.3, 146.3, 128.7, 123.6, 119.4, 112.9, 56.9, 36.2, 35.6, 26.6, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 17.0 min (minor), 18.7 min (major), 97% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-4-(3-methoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile (3i): $[\alpha]_D^{26}$ = +7.7 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (t, *J* = 8.0 Hz, 1H), 7.01 (s, 2H), 6.71-6.77 (m, 3H), 4.16 (s, 1H), 3.72 (s, 3H), 2.61-2.67 (m, 2H), 2.24-2.32 (m, 2H), 1.87-1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.7, 164.4, 159.0, 158.2, 146.2, 129.3, 119.5, 119.1, 113.6, 113.1, 111.2, 58.0, 54.8, 36.2, 35.1, 26.5, 19.8; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 11.6 min (minor), 14.1 min (major), 95% ee.

(*R*)-2-amino-4-(2-fluorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile (3j): $[\alpha]_D^{25}$ = –20.0 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09-7.25 (m, 4H), 7.04 (s, 2H), 4.47 (s, 1H), 2.61-2.63 (m, 2H), 2.21-2.30 (m, 2H), 1.891.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.1, 165.4, 159.1 (d, *J* = 31.0 Hz), 158.6, 131.5 (d, *J* = 12.5 Hz), 129.8 (d, *J* = 3.0 Hz), 128.7 (d, *J* = 7.5 Hz), 124.8 (d, *J* = 3.8 Hz), 119.8, 115.7 (d, *J* = 21.0 Hz), 112.7, 57.1, 36.7, 29.7, 26.9, 20.1; HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 27.2 min (minor), 32.4 min (major), 96% ee**.**

(*R*)-2-amino-5,6,7,8-tetrahydro-5-oxo-4-(thiophen-2-yl)-4*H*-chromene-3-carbonitrile (3k): $[\alpha]_D^{25}$ = +19.7 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30-7.31 (m, 1H), 7.11 (s, 2H), 6.90-6.92 (m, 1H), 6.84-6.85 (d, *J* = 0.7, 1H), 4.18 (s, 1H), 2.57-2.60 (m, 2H), 2.28-2.38 (m, 2H), 1.86-2.0 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.9, 164.4, 159.0, 149.2, 126.9, 124.4, 123.9, 119.6, 114.0, 57.8, 36.2, 30.2, 26.4, 19.7; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 10.6 min (minor), 12.5 min (major), 96% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-4-(naphthalen-2-yl)-5-oxo-4*H*-chromene-3-carbonitrile (3l): $[\alpha]_D^{25}$ = +10.3 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.51-7.77 (m, 3H), 7.25-7.45 (m, 2H), 6.98 (s, 2H), 5.17 (s, 1H), 2.62-2.75 (m, 2H), 2.18-2.32 (m, 2H), 1.91-2.01 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.9, 164.6, 158.5, 141.8, 133.1, 130.6, 128.1, 126.5, 125.5, 125.4, 124.8, 123.7, 119.5, 114.3, 58.6, 36.2, 30.0, 26.5, 19.9; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 13.0 min (minor), 15.6 min (major), 92% ee.

(*R*)-2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile (5): $[\alpha]_D^{25}$ = +21.0 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (t, *J* = 7.4 Hz, 2H), 7.14-7.20 (m, 3H), 7.00 (s, 2H), 4.18 (s, 1H), 2.50-2.55 (m, 2H), 2.12-2.28 (m, 2H), 1.10 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.0, 162.7, 158.6, 145.1, 128.7, 127.4, 127.0, 120.0, 113.1, 58.8, 55.1, 50.4,

36.0, 32.1, 28.6, 27.2; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 7.80 min (minor), 9.82 min (major), 90% ee.

(*R*)-2-amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-*c*]-chromene-3-carbonitrile (7): $[\alpha]_D^{25}$ = +12.7 (c = 1.0, acetone); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.41-7.51 (m, 4H), 7.25-7.33 (m, 5H), 4.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 157.1, 153.4, 152.1, 143.5, 132.9, 128.5, 127.7, 127.1, 124.7, 122.4, 119.2, 116.6, 112.9, 103.9, 57.9, 37.3; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel OD-H column, t_R = 23.55 min (minor), 30.61 min (major), 81% ee.

Gram Scale Procedure for the Michael Addition of 1,3-Cyclohexanedione (1) to Benzylidenemalonitriles (2a): To a stirred solution of benzylidenemalonitriles (**2a**, 0.925 g, 6.0 mmol) and binaphthyl-modified squaramide **IV** (21 mg, 30 μmol) in chloroform (20 mL) was added 1,3-cyclohexanedione (**1**, 0.673 g, 6.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was purified by column chromatography (EtOAc/1,2-dichloroethane = 1:25) to give the desired product **3a** (1.486 g, 93%).

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