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Organocatalytic conjugate addition promoted by multi-hydrogen-bond cooperation: access to chiral 2-amino-3-nitrile-chromenes†

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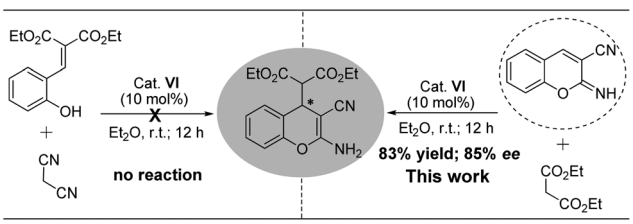
A new efficient enantioselective conjugate addition strategy has been disclosed to rapidly construct 2-amino-3-nitrile-chromene complexes *via* a multi-hydrogen-bond cooperative activation model.

Introduction

The importance of heterocycles has been fully demonstrated in medicinal chemistry. For example, a very large number of drug molecules contain heterocycles.[1] Therefore, the development of efficient methods for rapid construction of heterocycles has received great attention. In recent elegant reports, 2-amino-3-nitrile-chromenes have been proved to be an important class of heterocyclic compounds and indicated as common structural motifs in a diverse set of biologically important molecules,[2] such as mitogen-activated protein kinase inhibitors,[2e] tumor antagonists[2f] and anticancer drugs.[2g–i] Although a number of methods have been reported, these are mostly focused on racemic synthesis of 2-amino-3-nitrile-chromenes.[3] Given the fact that enantiomers often indicate distinct biological activity, the efficient access to optically pure 2-amino-3-nitrile-chromenes would be extremely desirable to further study the correlation between the chirality and their propensities for biological activities to acquire more potent and appropriate pharmaceutical candidates.[4] To date, examples on the enantioselective assembly of 2-amino-3-nitrile-chromene structures are still rather scarce.[5] Recently, Xie and co-workers reported an asymmetric reaction of α,β-unsaturated ketones with malononitrile to give chiral 2-amino-3-nitrile-chromenes with high enantioselectivities (up to 96% ee).[5a] Later, the Zhao group described 4*H*-chromene-3-carbonitrile and its derivatives synthesis *via* a cascade Michael-cyclization sequence.[5b,c] More recently, our group described a new example of an indane amine–thiourea organocatalyst catalyzed asymmetric reaction of *tert*butyl(2-hydroxyphenyl)-(phenylsulfonyl)methylcarbamate with malononitrile to afford similar 2-amino-3-nitrile-chromenes with good to excellent enantioselectivities.[5d] However, limited substrate scope and inconvenient starting materials preparation in the above examples largely reduce the synthetic attractiveness. Therefore, advantageous methodology in terms of enantioselectivity, starting materials availability, operational simplicity and high levels of functional group tolerance is still in high demand.

As part of our efforts toward the efficient synthesis of 2-amino-3-nitrile-chromenes, we decided to seek a new class of readily available starting materials. A designed Michael addition triggered cascade reaction of malononitrile with diethyl benzylidenemalonate was tested (Scheme 1). Nevertheless, none of the desired product was afforded (Scheme 1, no reaction). In this communication, we describe a new development of a valuable catalytic process to construct enantiomeric 2-amino-3-nitrile-chromenes through 2-iminochromenes and malonates (Scheme 1). Some noteworthy attributes of the system include reaction mildness (room temperature), easy-preparation of starting materials (note: one-step synthesis of



Scheme 1 Controlled experiments.

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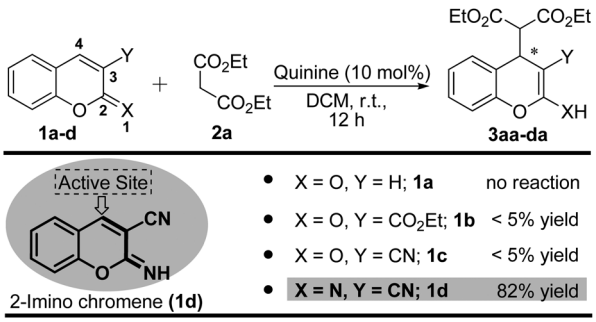
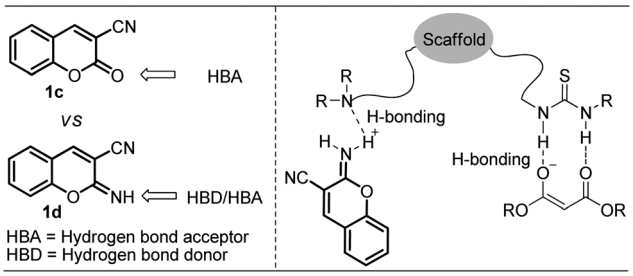


Scheme 2 Reaction feasibility investigation.



Scheme 3 Proposed catalytic model.

pure 2-iminochromenes with no flash chromatography), and high levels of stereo-control.

Results and discussion

In the course of our initial study, we made an interesting finding (Scheme 2): the use of coumarin (**1a**, X = O, Y = H) as an electrophile resulted in no formation of the desired product **3aa** in the presence of diethyl malonate **2a** and 10 mol% quinine as the catalyst. We envision that the electrophilicity of C4 may be the critical factor in this transformation. Then two other controlled experiments were examined *via* the introduction of more electron-withdrawing groups to the C3 of the coumarin skeleton. However, two designed substrates (**1b** (X = O, Y = CO_2Et) and **1c** (X = O, Y = CN)) both indicated no enhanced reactivity (Scheme 2, <5% yield). Surprisingly, if we use "NH" to replace "O" (**1c** *vs.* **1d**), the corresponding product **3da** was obtained with an 82% yield (Scheme 2). On the basis of structure difference of **1c** and **1d**, we envision that the "NH" group may provide an additional binding force to allow compound **1d** to react with nucleophile **2a** more efficiently. Based on the above assumption, we proposed a catalytic model (Scheme 3). In general, the compound **1c** can work as a hydrogen bond acceptor. However, the compound **1d** can work as not only a hydrogen bond acceptor, but also a hydrogen bond donor. As highlighted in Scheme 3, the tertiary amine functional group, a Brønsted base of the catalyst, can activate **1d** through two potential H-bondings. This multiple H-bondings cooperated catalytic model may lead ultimately to higher activity in the reaction.

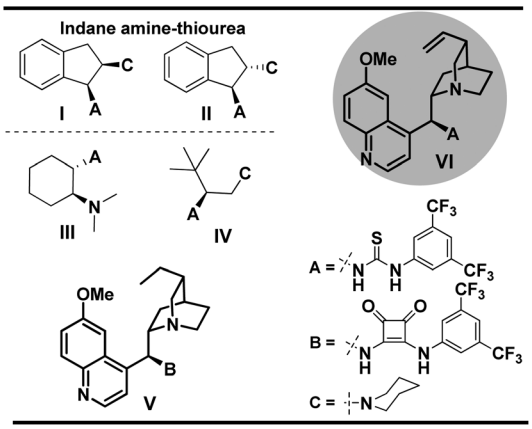
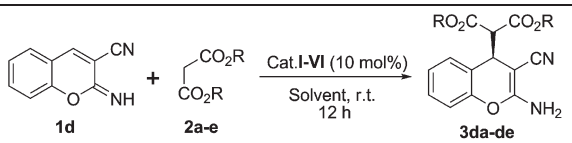


Fig. 1 Screened organocatalysts.

Table 1 Optimization of reaction conditions[a]

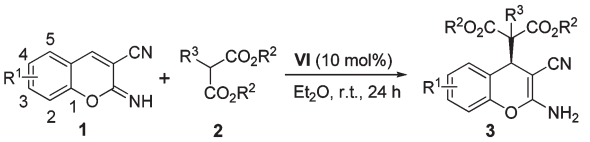


Entry	Cat.	Solvent	R	Yield[b] (%)	ee[c] (%)
1	**I**	CH_2Cl_2	Et (**2a**)	54	0
2	**II**	CH_2Cl_2	Et (**2a**)	74	31
3	**III**	CH_2Cl_2	Et (**2a**)	52	0
4	**IV**	CH_2Cl_2	Et (**2a**)	62	15
5	**V**	CH_2Cl_2	Et (**2a**)	82	−50
6	**VI**	CH_2Cl_2	Et (**2a**)	85	61
7	**VI**	Toluene	Et (**2a**)	85	60
8	**VI**	Anisole	Et (**2a**)	88	64
9	**VI**	THF	Et (**2a**)	90	81
10	**VI**	CPME[d]	Et (**2a**)	82	84
11	**VI**	Et_2O	Et (**2a**)	83	85
12	**VI**	Et_2O	Me (**2b**)	81	77
13[e]	**VI**	**Et_2O**	**i-Pr** (**2c**)	**85**	**94**
14	**VI**	Et_2O	*t*-Bu (**2d**)	<10	—[f]
15	**VI**	Et_2O	Bn (**2e**)	83	55

[a] Reaction condition: a mixture of **1d** (0.10 mmol), **2a–e** (0.30 mmol), Cat. (10 mol%) in DCM (0.5 mL) was stirred at room temperature for 12 h. [b] Isolated yield. [c] Determined by HPLC. [d] CPME refers to cyclopentyl methyl ether. [e] 24 h. [f] Not determined.

Next, we turned to explore an asymmetric version of 2-amino-3-nitrile-chromenes synthesis *via* chiral catalysts promoted Michael addition of malonates to 2-iminochromenes. Our initial investigation commenced with evaluating various organocatalysts (Fig. 1). Recently, our group reported a new indane amine–thiourea catalytic system (Fig. 1).[5d,6] Thereafter, we firstly sought to expand its usage to this new asymmetric transformation. As shown in Table 1, 2-iminochromene **1d** reacted with diethyl malonate **2a** in the presence of indane amine–thiourea catalysts **I–II**, but achieved low levels of enantioselectivity (entries 1–2, 0% ee and 31% ee, respectively). To enhance the enantiocontrol, some other bifunctional amine–thiourea catalysts **III–VI** (Fig. 1) were evaluated continuously. To our delight, the use of quinine–thiourea catalyst **VI**[7] resulted in a significantly improved enantioselectivity (Table 1,

Table 2 Substrate scope[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)	ee[c] (%)
1	H	i-Pr	H	**3dc**	85	94
2	4-Br	i-Pr	H	**3ec**	87	95
3	4-Cl	i-Pr	H	**3fc**	93	96
4	4-F	i-Pr	H	**3gc**	91	96
5	4-NO_2	i-Pr	H	**3hc**	92	96
6	4-Me	i-Pr	H	**3ic**	89	91
7	4-OMe	i-Pr	H	**3jc**	80	91
8	3-OMe	i-Pr	H	**3kc**	91	84
9	2-Allyl	i-Pr	H	**3lc**	81	89
10	2-Br-4-Cl	i-Pr	H	**3mc**	94	84
11	2,4-Br_2	i-Pr	H	**3nc**	88	84
12	2,4-Cl_2	i-Pr	H	**3oc**	81	82
13	4-Br	Et	H	**3ea**	90	86
14	2,4-Br_2	Et	H	**3na**	92	95
15	4-Br	Me	H	**3eb**	85	96
16	H	i-Pr	F	**3df**	91	95

[a] Reaction conditions: **1** (0.10 mmol), **2c** (0.30 mmol), **VI** (10 mol%), Et_2O (0.5 mL), room temperature, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC.

entry 6, 61% ee). Further optimization of other reaction parameters revealed that the solvent is one of the crucial factors for enantioselectivity. When the reaction was carried out in THF, cyclopentyl methyl ether (CPME) or Et_2O, the results were positively influenced, leading to the corresponding product **3da** in high yields and high ee values (Table 1, entries 9–11, 82–90% yield, 81–95% ee). After a comprehensive evaluation, Et_2O was finally selected as the ideal reaction medium for further optimization. In the process of further enhancing enantiocontrol, we found that the size of dialkyl malonates largely affected the results (entries 12–14). As highlighted in Table 1, a suitable size based diisopropyl malonate **2c** eventually supported the highest enantioselectivity (entry 13, 85% yield, 94% ee, 24 h).

With the optimized reaction conditions in hand, we then investigated the generality of 2-iminochromenes **1**. As presented in Table 2, the substitution pattern of 2-iminochromenes could be varied successfully: C4-substituted electron-withdrawing, neutral and electron-donating substituents were tolerated and demonstrated remarkably high yields and ees in all cases (entries 1–7, **3dc–jc**, 85–93% yield, 91–96% ee). In addition, substrates with electron-withdrawing and/or electron-donating substituents at the 2- or 3-position also showed high degrees of reactivities and enantioselectivities in generating the desired products (entries 8–12, **3kc–oc**). Notably, variation of dialkyl malonates **2** can also be tolerated in the reaction and gave a corresponding good result (entries 13–15, 85–92% yield, 86–96% ee). Moreover, 2-fluorated diisopropyl malonate **2f** also showed high activity and provided excellent enantiocontrol (entry 16, 91% yield, 95% ee). The absolute configuration of the products was determined by single-crystal X-ray analysis of **3na** (Fig. 2).[8]

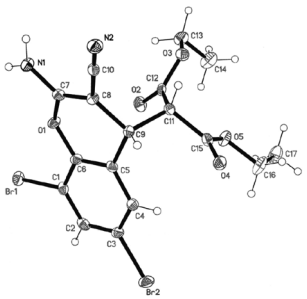


Fig. 2 X-ray crystal structure of **3na**.

Conclusions

In summary, we have developed a new efficient enantioselective conjugate addition of malonates to 2-iminochromenes mediated by a thiourea catalyst **VI**. The method generates 2-amino-3-nitrile-chromenes in good to excellent yields (80–94%) and with high levels of enantioselectivities (82–96% ee). It is worth noting that our method provides a rapid entry to 2-amino-3-nitrile-chromene complex structures from simple starting materials in a highly enantioselective manner. Further studies with respect to additional molecular complexity and mechanistic insights are in progress in our laboratory.

Experimental

General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in EI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T mass spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$ solution, or ninhydrin followed by heating using a heat gun. Flash chromatography separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral phase HPLC analysis. Optical rotations were recorded on a Jasco DIP-1000 polarimeter.

General procedure

To a solution of Et_2O (0.5 mL) were added chromene derivatives **1** (0.10 mmol), malonate **2** (0.30 mmol) and catalyst **VI** (0.01 mmol). The reaction mixture was stirred at room temperature for the time given and then the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel, eluting with hexane–EtOAc (10 : 1 to 5 : 1), to afford the desired product.

(*R*)-Diethyl 2-(2-amino-3-cyano-4*H*-chromen-4-yl)malonate (3da). Yellow oil. $[\alpha]_D^{25}$ = −1.5 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.29–7.28 (m, 1H), 7.25–7.21 (m, 1H), 7.11–7.10 (m, 1H), 7.00–6.97 (m, 1H), 4.73–4.72 (br, 2H), 4.39 (d, *J* = 9.0 MHz, 1H), 4.20–4.15 (m, 2H), 4.12–4.08 (m, 2H), 3.63 (d, *J* = 9.0 MHz, 1H), 1.26–1.14 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 167.1, 167.0, 162.3, 150.0, 128.7, 128.4, 124.9, 120.8, 119.4, 116.3, 61.7, 61.6, 58.9, 55.9, 35.5, 13.8, 13.7. MS (ESI) *m*/*z* [M + Na^+]: 352.91. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{17}H_{18}N_2O_5Na$) 353.1121, found *m*/*z* 353.1108. The enantiomeric excess was determined to be 85% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 9 : 1, 1.0 mL min^{-1}]: 38.8 min (major), 43.2 min (minor).

(*R*)-Dimethyl 2-(2-amino-3-cyano-4*H*-chromen-4-yl)malonate (3db). Yellow oil. $[\alpha]_D^{25}$ = +4.1 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.24–7.23 (m, 2H), 7.13–7.10 (m, 1H), 7.01–6.99 (m, 1H), 4.78–4.77 (br, 2H), 4.39–4.37 (m, 1H), 3.73 (s, 3H), 3.66–3.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 167.4, 162.4, 150.0, 128.8, 128.2, 125.0, 120.7, 119.3, 116.4, 58.6, 55.7, 52.6, 52.5, 35.8. MS (ESI) *m*/*z* [M + Na^+]: 324.92. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{15}H_{14}N_2O_5Na$) 325.0801, found *m*/*z* 325.0795. The enantiomeric excess was determined to be 77% by HPLC. [OJ-H column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 18.9 min (minor), 24.5 min (major).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-4*H*-chromen-4-yl)malonate (3dc). Yellow oil. $[\alpha]_D^{25}$ = +11.8 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.33–7.32 (m, 1H), 7.25–7.22 (m, 1H), 7.11–7.09 (m, 1H), 6.97–6.96 (m, 1H), 5.06–5.04 (m, 1H), 4.94–4.92 (m, 1H), 4.73–4.72 (br, 2H), 4.38 (d, *J* = 5.0 MHz, 1H), 3.59 (d, *J* = 5.0 MHz, 1H), 1.22–1.20 (m, 6H), 1.13–1.11 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.9, 166.5, 161.9, 150.0, 128.6, 128.5, 124.8, 120.7, 116.2, 69.3, 69.2, 59.2, 56.4, 35.1, 21.5, 21.4, 21.3, 21.2. MS (ESI) *m*/*z* [M + Na^+]: 381.01. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{22}N_2O_5Na$) 381.1437, found *m*/*z* 381.1421. The enantiomeric excess was determined to be 94% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 11.3 min (major), 14.3 min (minor).

(*R*)-Dibenzyl 2-(2-amino-3-cyano-4*H*-chromen-4-yl)malonate (3de). Yellow oil. $[\alpha]_D^{25}$ = −3.2 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.31–7.26 (m, 6H), 7.23–7.15 (m, 6H), 7.03–7.00 (m, 1H), 6.93–6.91 (m, 1H), 5.18–5.06 (m, 4H), 4.66–4.65 (br, 2H), 4.28 (d, *J* = 5.5 MHz, 1H), 3.60 (d, *J* = 5.0 MHz, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.8, 166.7, 162.3, 149.9, 135.1, 135.0, 128.9, 128.8, 128.5, 128.4, 128.3, 125.0, 124.5, 120.4, 119.4, 116.4, 67.5, 67.4, 58.8, 55.7, 35.7. MS (ESI) *m*/*z* [M + Na^+]: 476.91. HRMS (ESI): exact mass calculatd for [M + Na^+] ($C_{27}H_{22}N_2O_5Na$) 477.1422, found *m*/*z* 477.1421. The enantiomeric excess was determined to be 55% by HPLC. [IC column, 254 nm, *n*-hexane : IPA = 9 : 1, 1.0 mL min^{-1}]: 47.6 min (minor), 54.0 min (major).

(*R*)-Diisopropyl 2-(2-amino-6-bromo-3-cyano-4*H*-chromen-4-yl)malonate (3ec). Yellow oil. $[\alpha]_D^{25}$ = +4.6 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.46–7.45 (m, 1H), 7.36–7.32 (m, 1H), 6.86 (d, *J* = 14.5 MHz, 1H), 5.12–5.03 (m, 1H), 4.98–4.90 (m, 1H), 4.79–4.78 (br, 2H), 4.33 (d, *J* = 8.5 MHz, 1H), 3.59 (d, *J* = 8.5 MHz, 1H), 1.25–1.21 (m, 6H), 1.15–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.7, 166.4, 161.7, 149.2, 131.6, 131.3, 122.8, 119.0, 117.9, 117.2, 69.7, 69.4, 59.0, 56.2, 35.0, 21.6, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 460.89. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{21}BrN_2O_5Na$) 459.0536, found *m*/*z* 459.0526. The enantiomeric excess was determined to be 95% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 9.1 min (major), 10.3 min (minor).

(*R*)-Diisopropyl 2-(2-amino-6-chloro-3-cyano-4*H*-chromen-4-yl)-malonate (3fc). Yellow oil. $[\alpha]_D^{25}$ = +2.5 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.31–7.30 (m, 1H), 7.20–7.17 (m, 1H), 6.91 (d, *J* = 14.5 MHz, 1H), 5.11–5.03 (m, 1H), 4.97–4.89 (m, 1H), 4.85–4.84 (br, 2H), 4.32 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.24–1.22 (m, 6H), 1.15–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.7, 166.4, 161.8, 148.6, 129.7, 128.6, 128.3, 122.3, 117.5, 69.7, 69.4, 58.9, 55.9, 35.0, 21.5, 21.4, 21.3, 21.2. MS (ESI) *m*/*z* [M + Na^+]: 414.97. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{21}ClN_2O_5Na$) 415.1030, found *m*/*z* 415.1031. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 8.7 min (major), 10.0 min (minor).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-6-fluoro-4*H*-chromen-4-yl)-malonate (3gc). Yellow oil. $[\alpha]_D^{23}$ = +21.4 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 7.08 (d, *J* = 8.5 MHz, 1H), 6.93 (d, *J* = 5.5 MHz, 2H), 5.09–5.04 (m, 1H), 4.95–4.90 (m, 1H), 4.81–4.80 (br, 2H), 4.34 (d, *J* = 4.5 MHz, 1H), 3.58 (d, *J* = 4.5 MHz, 1H), 1.24–1.22 (m, 6H), 1.13–1.11 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.8, 166.5, 162.0, 160.0, 158.1, 146.2, 122.4, 122.3, 119.3, 117.6, 117.5, 115.3 (q, *J* = 45.0 MHz, 1H), 69.7, 69.4, 59.0, 55.8, 35.3, 21.6, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 398.98. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{21}FN_2O_5Na$) 399.1333, found *m*/*z* 399.1327. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 8.7 min (major), 9.7 min (minor).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-6-nitro-4*H*-chromen-4-yl)malonate (3hc). Yellow oil. $[\alpha]_D^{25}$ = −4.6 (*c* = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 8.27–8.26 (m, 1H), 8.16–8.13 (m, 1H), 7.12 (d, *J* = 15.0 MHz, 1H), 5.12–5.08 (m, 1H), 4.97–4.92 (m, 3H), 4.45 (d, *J* = 7.5 MHz, 1H), 3.68 (d, *J* = 7.5 MHz, 1H), 1.28–1.22 (m, 6H), 1.17–1.13 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 166.6, 166.3, 161.0, 154.3, 144.4, 124.7, 124.4, 121.9, 118.4, 117.2, 70.2, 69.7, 58.6, 56.2, 35.0, 21.6, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 426.01. HRMS (ESI):

exact mass calculated for [M + Na^+] ($C_{19}H_{21}N_3O_7Na$) 426.1275, found *m*/*z* 426.1272. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 13.4 min (minor), 15.7 min (major).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-6-methyl-4*H*-chromen-4-yl)-malonate (3ic). Yellow oil. $[\alpha]_D^{25}$ = +3.8 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.09–7.08 (m, 1H), 7.02–7.01 (m, 1H), 6.85 (d, *J* = 9.0 MHz, 1H), 5.08–5.03 (m, 1H), 4.97–4.92 (m, 1H), 4.87–4.86 (br, 2H), 4.33 (d, *J* = 5.0 MHz, 1H), 3.58 (d, *J* = 5.0 MHz, 1H), 2.28 (s, 3H), 1.23–1.22 (m, 6H), 1.15–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.7, 162.2, 148.0, 134.4, 129.2, 128.7, 120.4, 119.6, 115.9, 69.4, 69.2, 59.3, 56.4, 35.3, 21.6, 21.5, 21.4, 20.7. MS (ESI) *m*/*z* [M + Na^+]: 395.00. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{20}H_{24}N_2O_5Na$) 395.1581, found *m*/*z* 395.1577. The enantiomeric excess was determined to be 91% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 11.1 min (major), 15.8 min (minor).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-6-methoxy-4*H*-chromen-4-yl)-malonate (3jc). Yellow oil. $[\alpha]_D^{25}$ = +0.6 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.03–7.00 (m, 1H), 6.87 (d, *J* = 7.5 MHz, 1H), 6.81 (d, *J* = 7.5 MHz, 1H), 5.05–5.03 (m, 1H), 4.95–4.91 (m, 3H), 4.36 (d, *J* = 5.0 MHz, 1H), 3.84 (s, 3H), 3.55 (d, *J* = 5.0 MHz, 1H), 1.22–1.20 (m, 6H), 1.15–1.10 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.8, 166.6, 162.2, 147.3, 139.6, 124.5, 122.0, 119.9, 119.5, 110.9, 69.3, 69.2, 59.4, 55.9, 35.3, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 410.93. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{20}H_{24}N_2O_6Na$) 411.1537, found *m*/*z* 411.1527. The enantiomeric excess was determined to be 91% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 16.1 min (major), 20.2 min (minor).

(*R*)-Diisopropyl 2-(2-amino-3-cyano-7-methoxy-4*H*-chromen-4-yl)-malonate (3kc). Yellow oil. $[\alpha]_D^{25}$ = +1.6 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.24–7.22 (m, 1H), 6.67–6.63 (m, 1H), 6.50 (d, *J* = 4.0 MHz, 1H), 5.07–5.03 (m, 1H), 4.95–4.91 (m, 1H), 4.71–4.70 (br, 2H), 4.32 (d, *J* = 8.0 MHz, 1H), 3.77 (s, 3H), 3.57 (d, *J* = 8.0 MHz, 1H), 1.23–1.21 (m, 6H), 1.15–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.1, 166.7, 161.9, 159.8, 150.7, 129.3, 119.5, 112.6, 111.0, 101.6, 69.3, 69.1, 59.2, 56.9, 55.9, 55.4, 34.6, 21.6, 21.5, 21.4. MS (ESI) *m*/*z* [M + Na^+]: 410.94. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{20}H_{24}N_2O_6Na$) 411.1529, found *m*/*z* 411.1527. The enantiomeric excess was determined to be 84% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 14.2 min (major), 19.5 min (minor).

(*R*)-Diisopropyl 2-(8-allyl-2-amino-3-cyano-4*H*-chromen-4-yl)malonate (3lc). Yellow oil. $[\alpha]_D^{25}$ = +6.2 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.19–7.17 (m, 1H), 7.09–7.08 (m, 1H), 7.05–7.03 (m, 1H), 5.94–5.89 (m, 1H), 5.08–5.00 (m, 3H), 4.94–4.91 (m, 1H), 4.75–4.74 (br, 2H), 4.37 (d, *J* = 5.5 MHz, 1H), 3.55–3.51 (m, 1H), 3.45–3.35 (m, 2H), 1.23–1.21 (m, 6H), 1.15–1.10 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.7, 162.2, 148.1, 135.8, 129.4, 127.3, 127.2, 126.8, 124.6, 121.0, 119.5, 117.1, 116.2, 69.4, 69.3, 59.5, 56.7, 35.5, 33.8, 33.1, 21.6, 21.4. MS (ESI) *m*/*z* [M + Na^+]: 421.00. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{22}H_{26}N_2O_5Na$) 421.1740, found *m*/*z* 421.1734. The enantiomeric excess was determined to be 89% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 8.6 min (major), 10.9 min (minor).

(*R*)-Diisopropyl 2-(2-amino-8-bromo-6-chloro-3-cyano-4*H*-chromen-4-yl)malonate (3mc). Yellow oil. $[\alpha]_D^{25}$ = +6.2 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.47 (d, *J* = 4.0 MHz, 1H), 7.30 (d, *J* = 4.0 MHz, 1H), 5.12–5.04 (m, 1H), 4.99–4.92 (m, 3H), 4.34 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.26–1.23 (m, 6H), 1.16–1.12 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.6, 166.2, 161.6, 145.9, 131.9, 130.0, 127.7, 123.8, 118.5, 110.8, 69.9, 69.6, 59.0, 56.5, 35.6, 21.6, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 492.85. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{20}BrClN_2O_5Na$) 493.0137, found *m*/*z* 493.0136. The enantiomeric excess was determined to be 84% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 85 : 15, 1.0 mL min^{-1}]: 9.5 min (major), 11.9 min (minor).

(*R*)-Diisopropyl 2-(2-amino-6,8-dibromo-3-cyano-4*H*-chromen-4-yl)-malonate (3nc). Yellow oil. $[\alpha]_D^{25}$ = +5.8 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, *J* = 4.0 MHz, 1H), 7.44 (d, *J* = 4.0 MHz, 1H), 5.10–5.06 (m, 1H), 4.97–4.93 (m, 3H), 4.34 (d, *J* = 8.5 MHz, 1H), 3.58 (d, *J* = 8.5 MHz, 1H), 1.26–1.23 (m, 6H), 1.16–1.13 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.6, 166.2, 161.6, 146.4, 134.7, 130.6, 124.3, 118.5, 117.2, 111.1, 70.0, 69.6, 59.1, 56.6, 35.5, 21.6, 21.5, 21.4, 21.3. MS (ESI) *m*/*z* [M + Na^+]: 533.66. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{20}Br_2N_2O_5Na$) 536.9629, found *m*/*z* 536.9631. The enantiomeric excess was determined to be 84% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 7.7 min (major), 9.6 min (minor).

(*R*)-Diisopropyl 2-(2-amino-6,8-dichloro-3-cyano-4*H*-chromen-4-yl)malonate (3oc). Yellow oil. $[\alpha]_D^{25}$ = +1.6 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.32–7.31 (m, 1H), 7.27–7.26 (m, 1H), 5.10–5.08 (m, 1H), 4.97–4.94 (m, 1H), 4.84–4.83 (br, 2H), 4.36 (d, *J* = 5.0 MHz, 1H), 3.59 (d, *J* = 5.0 MHz, 1H), 1.26–1.21 (m, 6H), 1.16–1.14 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.5, 166.1, 161.4, 144.8, 129.6, 129.0, 126.9, 123.8, 122.3, 118.4, 69.9, 69.5, 58.9, 56.4, 35.4, 21.5, 21.4, 21.3, 21.2. MS (ESI) *m*/*z* [M + Na^+]: 448.93. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{19}H_{20}Cl_2N_2O_5Na$) 449.0649, found *m*/*z* 449.0641. The enantiomeric excess was determined to be 82%, 81% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 7.2 min (major), 8.9 min (minor).

(*R*)-Diethyl 2-(2-amino-3-cyano-4*H*-chromen-4-yl)-2-fluoromalonate (3df). Yellow oil. $[\alpha]_D^{25}$ = +10.8 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.33–7.30 (m, 1H), 7.24–7.21 (m, 1H), 7.15–7.10 (m, 1H), 7.06–7.03 (m, 1H), 4.93–4.92 (br, 2H), 4.63 (d, *J* = 20.5 MHz, 1H), 4.42–4.35 (m, 2H), 4.27–4.19 (m, 2H), 1.36 (t, *J* = 12.0 MHz, 3H), 1.23 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 164.1, 151.2, 129.4, 128.4, 125.0, 118.9, 117.6, 116.7, 97.5, 95.8, 63.2, 62.9, 60.4, 51.8, 41.6, 41.4, 21.0, 14.2, 13.8. MS (ESI) *m*/*z* [M + Na^+]: 370.89. HRMS (ESI): exact mass calculated for [M + Na^+]

($C_{17}H_{17}FN_2O_5Na$) 371.1021, found *m*/*z* 371.1014. The enantiomeric excess was determined to be 86%, 95% by HPLC. [IC column, 254 nm, *n*-hexane : IPA = 9 : 1, 1.0 mL min^{-1}]: 44.2 min (minor), 48.9 min (major).

(*R*)-Diethyl 2-(2-amino-6-bromo-3-cyano-4*H*-chromen-4-yl)malonate (3ea). Yellow oil. $[\alpha]_D^{25}$ = +7.0 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.42–7.41 (m, 1H), 7.37–7.33 (m, 1H), 6.87 (d, *J* = 14.0 MHz, 1H), 4.83–4.82 (br, 2H), 4.33 (d, *J* = 9.0 MHz, 1H), 4.24–4.10 (m, 4H), 3.62 (d, *J* = 9.0 MHz, 1H), 1.25 (t, *J* = 12.0 MHz, 3H), 1.18 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.9, 166.8, 161.9, 149.1, 131.6, 131.1, 122.8, 118.9, 117.9, 117.2, 61.8, 61.7, 58.6, 55.7, 35.2, 13.8, 13.7. MS (ESI) *m*/*z* [M + Na^+]: 430.83. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{17}H_{17}BrN_2O_5Na$) 431.0220, found *m*/*z* 431.0213. The enantiomeric excess was determined to be 86% by HPLC. [IC column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 12.3 min (major), 14.1 min (minor).

(*R*)-Diethyl 2-(2-amino-6,8-dibromo-3-cyano-4*H*-chromen-4-yl)malonate (3na). Yellow oil. $[\alpha]_D^{25}$ = +7.8 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.61 (d, *J* = 3.5 MHz, 1H), 7.37 (d, *J* = 3.5 MHz, 1H), 5.05–5.04 (br, 2H), 4.30 (d, *J* = 9.0 MHz, 1H), 4.25–4.08 (m, 4H), 3.60 (d, *J* = 9.0 MHz, 1H), 1.26 (t, *J* = 12.0 MHz, 3H), 1.18 (t, *J* = 12.0 MHz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 166.7, 166.6, 161.8, 146.4, 134.7, 130.4, 124.2, 117.2, 111.1, 62.0, 61.8, 58.6, 55.9, 35.7, 13.8, 13.7. MS (ESI) *m*/*z* [M − H]$^-$: 485.96. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{17}H_{16}Br_2N_2O_5Na$) 508.9333, found *m*/*z* 508.9318. The enantiomeric excess was determined to be 95% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 4 : 1, 1.0 mL min^{-1}]: 9.5 min (major), 10.9 min (minor).

(*R*)-Dimethyl 2-(2-amino-6-bromo-3-cyano-4*H*-chromen-4-yl)malonate (3eb). Yellow oil. $[\alpha]_D^{25}$ = +9.0 (*c* = 0.50, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.36–7.34 (m, 2H), 6.90–6.87 (m, 1H), 4.91–4.90 (br, 2H), 4.31 (d, *J* = 10.0 MHz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.63 (d, *J* = 10.0 MHz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 167.2, 167.1, 162.1, 149.1, 131.7, 130.9, 122.7, 118.0, 117.3, 58.2, 55.1, 52.7, 52.6, 35.5. MS (ESI) *m*/*z* [M + Na^+]: 404.73. HRMS (ESI): exact mass calculated for [M + Na^+] ($C_{15}H_{13}BrN_2O_5Na$) 402.9894, found *m*/*z* 402.9900. The enantiomeric excess was determined to be 96% by HPLC. [ID column, 254 nm, *n*-hexane : IPA = 9 : 1, 1.0 mL min^{-1}]: 32.2 min (major), 33.4 min (minor).

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