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Enantioselective synthesis of naphthopyran derivatives catalyzed by bifunctional thiourea-tertiary amines

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Abstract—An efficient bifunctional thiourea catalyzed addition–cyclization reaction of 2-naphthol with α,α-dicyanoolefins is realized under mild conditions to afford the corresponding naphthopyran derivatives in high yields and moderate enantioselectivities. Additionally, the development of an asymmetric three-component one-pot procedure for the synthesis of naphthopyran derivatives is also reported.

1. Introduction

Benzo- and naphthopyran derivatives are an important class of heterocyclic compounds possessing biological and pharmacological activities, such as anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactin activities.[1] Some of these compounds can also be employed as cosmetics and pigments and as potential biodegradable agrochemicals.[2] Therefore, the synthesis of such compounds has attracted strong interest.[3] Several conventional syntheses of these polyfunctionalized benzopyrans involving the condensation of malononitrile with an aldehyde and phenol or naphthol using bases or amides as catalysts have been well-developed.[3] However, to the best of our knowledge, no asymmetric synthesis of naphthopyran derivatives has yet been reported.

On the other hand, over the last decade, a broad range of synthetically useful reactions employing the chiral *N*,*N*-dialkyl (thio) urea derivatives as active organocatalysts have been explored.[4] In the domain of urea and thiourea catalysts, remarkable advances were made by Jacobsen and Takemoto in a series of asymmetric reactions promoted by urea or thiourea containing a Schiff base or tertiary amine moiety as catalysts.[5] Based on these studies and bearing in mind that α,α-dicyanoolefins[6] and 2-naphthols[7] are suitable for acid and base activation, respectively (Fig. 1), we assumed that a chiral bifunctional catalyst may lead to an asymmetric version of the synthesis of naphthopyran derivatives. Herein, we report the first enantioselective addition of 2-naphthol to α,α-dicyanoolefins catalyzed by thiourea and tertiary amine-based bifunctional catalysts.

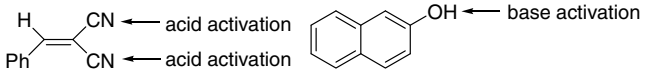

Figure 1.

2. Results and discussion

Using the reaction of 2-benzylidenemalononitrile with 2-naphthol as a model reaction, a series of thiourea and tertiary amine-based bifunctional catalysts (Fig. 2) were screened at room temperature in CH_2Cl_2, and the results are summarized in Table 1 (entries 1–7). Both the cinchona alkaloids and prolinol derived thiourea catalysts **1a**, **1b** and **1g** provided poor results. Of all the catalysts examined, the (*R*,*R*)-1,2-cyclohexyldiamine derived **1c** bearing a 3,5-bis(trifluoromethyl)phenyl substituent exhibited the highest enantioselectivity and yield (entry 3, 67% ee, and 89%

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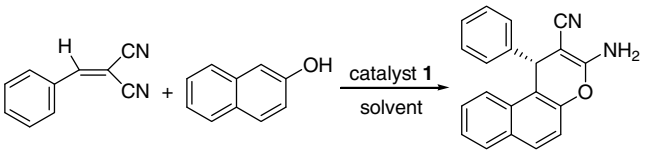
Table 1. Screening of the optimal reaction conditions for **2a** and **3a** in the presence of **1**[a]



2a **3a** **4a**

Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	CH_2Cl_2	86	8
2	**1b**	CH_2Cl_2	82	24
3	**1c**	CH_2Cl_2	89	67
4	**1d**	CH_2Cl_2	65	46
5	**1e**	CH_2Cl_2	75	43
6	**1f**	CH_2Cl_2	58	23
7	**1g**	CH_2Cl_2	88	25
8[d]	**1c**	CH_2Cl_2	72	58
9[d]	**1c**	Toluene	68	40
10[d]	**1c**	CH_3CN	53	13
11[d]	**1c**	THF	10	<5
12[d]	**1c**	*n*-Hexane	67	17
13[d]	**1c**	Et_2O	32	22
14[e]	**1c**	CH_2Cl_2	98	68
15[f]	**1c**	CH_2Cl_2	83	61

[a] Unless otherwise noted, the reaction was conducted with 0.2 mmol of **2a** and 0.2 mmol of **3a** in the presence of 20 mol % of **1** in 1.0 mL of solvent at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis on a chiral OD column.
[d] 10 mol % of **1** was used.
[e] 30 mg of 4 Å MS was added.
[f] The reaction was conducted at 0 °C and 30 mg of 4 Å MS was added.

yield). Changing the trifluoromethyl phenyl substituent in **1c** to phenyl **1d**, 4-fluorophenyl **1e** or cyclohexyl **1f** all led to inferior chemical yields and enantioselectivies. Next, the solvent, temperature and catalyst loading were examined with catalyst **1c** in order to improve the enantioselectivity. Unfortunately, poor enantioselectivity was obtained for all the other five solvents selected with lower yields (entries 9–13). A slightly better result was obtained when 4 Å molecular sieves were added to the reaction system (entry 14), however, no beneficial effect on the enantioselectivity was observed at 0 °C (entry 15, 61% ee).

With the optimized reaction conditions in hand, the scope of the reaction of α,α-dicyanoolefins with 2-naphthol was probed and the results are summarized in Table 2. Generally, all the arylidenemalononitriles examined could proceed smoothly to give the desired products (Table 2, entries 2–16). It was found that substrates with electron-donating groups on the phenyl ring, such as **2g** with a 4-methoxyphenyl group or **2m** with a furyl group, provided lower yields than the electron-withdrawing group substituted ones, although no significant decrease in ee values was observed (Table 2, entries 9 and 15). Moreover, a much lower yield (19%) was obtained for an alkyl substituted substrate **2n** with a comparable enantioselectivity to the aromatic ones. (Table 2, entry 16).[8] In addition, a substituted, naphthol 7-methoxy-2-naphthol, was also examined in this reaction with a much lower enantioselectivity achieved; what was more striking was that when 1-naphthol was used, only the racemic product **4b** was obtained (Table 2, entries 6 and 2), which revealed that the structures of the naphthols should have great influence on the enantioselectivity of this reaction.[9] The enantioselectivity of these products could be improved upon simple recrystallization. For example, the ee of **4c** increased up to 99% just through a single recrystallization in ethanol. The absolute configuration of the product **4c** was determined to be (*S*)- by X-ray crystallographic analysis (Fig. 3).[10]

Furthermore, since the one-pot three-component synthesis of naphthopyran derivatives from aldehydes, malononitrile

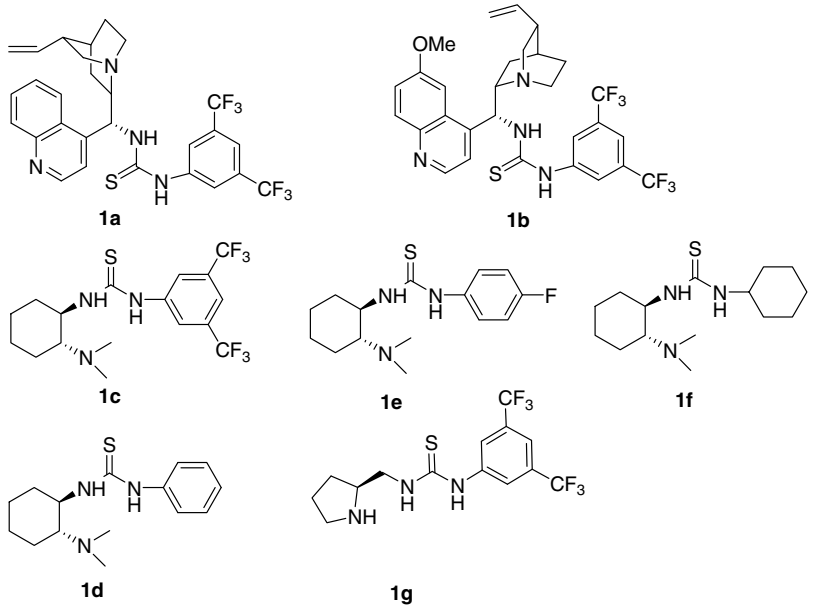
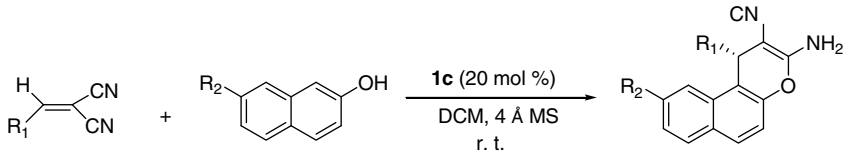


Figure 2. Thiourea-tertiary amine catalysts used in the study.

Table 2. Enantioselective synthesis of naphthopyran derivatives catalyzed by **1c**[a]



2a-n **3a-b** **4a-p**

Entry	2	R_1	R_2	Product	Yield[b] (%)	ee[c] (%)
1	**2a**	C_6H_4	H (**3a**)	**4a**	98	68
2	**2a**	C_6H_4	1-Naphthol	**4b**	86	—
3	**2b**	4-BrC_6H_4	H (**3a**)	**4c**	87	71 (>99)[d]
4	**2c**	4-ClC_6H_4	H (**3a**)	**4d**	93	67
5	**2d**	4-FC_6H_4	H (**3a**)	**4e**	75	90
6	**2d**	4-FC_6H_4	CH_3O (**3b**)	**4f**	91	66
7	**2e**	4-$CH_3C_6H_4$	H (**3a**)	**4g**	83	79
8	**2f**	4-$NO_2C_6H_4$	H (**3a**)	**4h**	98	65
9	**2g**	4-$CH_3OC_6H_4$	H (**3a**)	**4i**	38	62
10	**2h**	2,4-$Cl_2C_6H_3$	H (**3a**)	**4j**	99	56
11	**2i**	3-FC_6H_4	H (**3a**)	**4k**	98	70
12	**2j**	3-$CH_3OC_6H_4$	H (**3a**)	**4l**	94	76
13	**2k**	2-ClC_6H_4	H (**3a**)	**4m**	94	84
14	**2l**	3-ClC_6H_4	H (**3a**)	**4n**	94	65
15	**2m**	2-Furyl	H (**3a**)	**4o**	52	61
16	**2n**	*n*-Hexyl	H (**3a**)	**4p**	19	57

[a] Unless otherwise noted, the reaction was conducted with 0.2 mmol of **2** and 0.2 mmol of **3** in the presence of 20 mol % of **1c** in 1.0 mL of DCM at room temperature and 30 mg of 4 Å MS was added.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis on a chiral OD-H column. The absolute configuration of the product **4c** was determined to be (*S*)- by X-ray crystallographic analysis and the others **4a**, **4d**–**4p** were assigned by assuming that a similar catalytic mechanism was followed.
[d] After a single recrystallization from 95% ethanol.

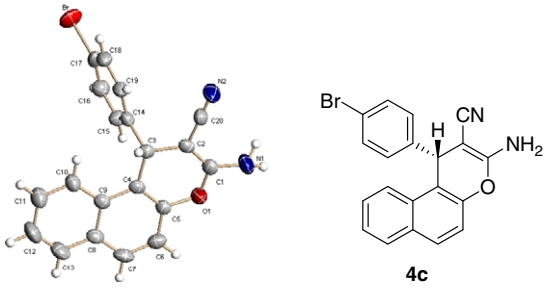


Figure 3. X-ray structure of compound **4c**.

and 2-naphthol have been reported,[3d] we conceived that an asymmetric version of this procedure may also be possible. Indeed, the reactions could proceed smoothly as expected to provide the desired products in good yields albeit with lower enantioselectivities than the above stepwise procedure. Various substituted phenyl aldehydes were reacted with malononitrile and 2-naphthol to study the scope of this one-pot procedure (Table 3). In general, electron-deficient aldehydes reacted well to give the corresponding naphthopyran derivatives in good to excellent yields and moderate enantioselectivities (Table 3, entries 2–4 and 6–8). However, lower enantioselectivities were observed when electron-rich aryl aldehydes were used (entries 1 and 5).

3. Conclusions

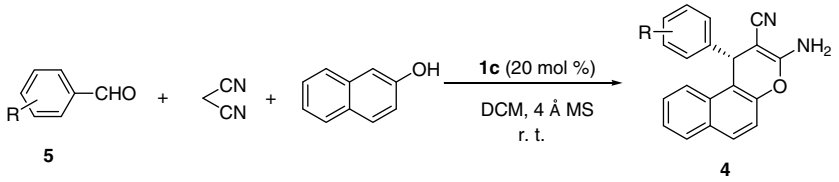
In conclusion, we have reported the first enantioselective synthesis of naphthopyran derivatives catalyzed by chiral bifunctional thiourea-tertiary amine compounds. Moderate to excellent enantioselectivities (56–90% ee) have been achieved with high isolated yields. Moreover, the enantioselective synthesis of naphthopyran derivatives via a one-pot three-component condensation of malnonitrile with aldehyde and 2-naphthol were also explored.

4. Experimental

4.1. General

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. Flash column chromatography was performed using silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. The ^1H NMR spectra were recorded on a DPX-300 or Varian EM-360 (300 MHz). All chemical shifts (δ) are given in ppm. Data are reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz). ^{13}C NMR spectra were recorded on a DPX-300 (75 MHz). Analytical high performance liquid chromatography (HPLC) was carried out on WATERS equipment using a chiral column. Melting points were determined on a SGW X-4 apparatus

Table 3. Asymmetric one-pot synthesis of naphthopyran derivatives catalyzed by **1c**[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	H	**4a**	72	33
2	4-Br	**4c**	81	65
3	4-Cl	**4d**	90	55
4	4-F	**4e**	71	62
5	4-Me	**4g**	67	37
6	4-NO_2	**4h**	91	55
7	2-Cl	**4m**	75	56
8	3-Cl	**4n**	93	52

[a] Unless otherwise noted, the reaction was conducted with 0.2 mmol of **5**, 0.2 mmol of malononitrile and 0.2 mmol of 2-naphthol in the presence of 20 mol % of **1c** in 1.0 mL of DCM at room temperature and 30 mg of 4 Å MS was added.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis on a chiral OD-H column. The absolute configuration of product **4c** was determined to be (*S*) by X-ray crystallographic analysis and the others **4a**, **4d**–**4n** were assigned by assuming that a similar catalytic mechanism was followed.

and were/are uncorrected. Optical rotations were measured on a JASCO P-1010 Polarimeter at $\lambda = 589$ nm. IR spectra were recorded on a Perkin–Elmer 983G instrument. Elementary analysis was taken on a Vario EL III elementary analysis instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

Catalysts **1a**,[11a] **1b**,[11b] **1c**,[5f] **1d**,[5f] **1e**,[6a] **1f**[11b] and **1g**[11c] were synthesized according to references.

4.1.1. General procedure for the asymmetric synthesis of naphthopyran derivatives 4a–4o. To a solution of 0.2 mmol of 2-naphthol and 0.2 mmol of α,α-dicyanoolefins in the presence of 20 mol % of **1c** in 1.0 mL of DCM at room temperature, 30 mg of 4 Å MS was added. Stirring at room temperature was continued for 6–48 h. The crude mixture was purified by column chromatography on silica gel to afford the corresponding products.

4.1.2. 3-Amino-1-phenyl-1*H*-benzo[*f*]chromene-2-carbonitrile 4a.[12a] White solid. Mp 278–279 °C; $[\alpha]_D^{23.8} = -5.2$ (*c* 1.15, DMSO);[12] ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96–7.90 (m, 2H), 7.85 (d, $J = 4.5$ Hz, 1H), 7.47–7.13 (m, 8H); 7.0 (s, 1H), 5.30 (s, 1H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD column (25 °C, 254 nm, 4:1, hexane/2-propanol, 0.6 mL/min); $t_{major} = 18.24$ min, $t_{minor} = 31.29$ min.

4.1.3. 3-Amino-1-(4-bromophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4c.[12a] White solid. Mp 221–222 °C; $[\alpha]_D^{27.7} = -57.3$ (*c* 0.93, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2H), 7.60–7.59 (m, 1H), 7.39–7.36 (m, 3H), 7.26–7.22 (m, 2H), 7.07–7.04 (m, 2H), 5.20 (d, $J = 4.5$ Hz, 1H), 4.63 (s, 1H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 9.65$ min, $t_{minor} = 14.87$ min.

4.1.4. 3-Amino-1-(4-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4d.[12a] White solid. Mp 210–211 °C; $[\alpha]_D^{24.8} = -43.9$ (*c* 0.70, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H), 7.63–7.59 (m, 1H), 7.42–7.40 (m, 2H); 7.27–7.21 (m, 3H), 7.11 (d, $J = 8.3$ Hz, 2H), 5.23 (s, 1H), 4.62 (s, 1H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 8.31$ min, $t_{minor} = 11.34$ min.

4.1.5. 3-Amino-1-(4-fluorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4e.[12a] White solid. Mp 237–238 °C; $[\alpha]_D^{27.1} = -2.8$ (*c* 0.64, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H), 7.65–7.63 (m, 1H), 7.40 (dd, $J = 2.8$ Hz, 2H), 7.25 (d, $J = 6.8$ Hz, 1H), 7.17–7.12 (m, 2H), 6.94 (t, $J = 8.6$ Hz, 2H), 5.24 (s, 1H), 4.62 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 9.26$ min, $t_{minor} = 14.71$ min.

4.1.6. 3-Amino-1-(4-fluorophenyl)-9-methoxy-1*H*-benzo[*f*]-chromene-2-carbonitrile 4f. White solid. Mp 238–239 °C; $[\alpha]_D^{24.6} = -51.35$ (*c* 0.54, DMSO); IR (KBr) $\nu = 3465$, 3359, 2183, 1662, 1654, 1592, 1509, 1408, 1239, 1218, 827 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (t, $J = 18.2$ Hz, 2H), 7.19–7.02 (m, 4H), 6.96 (t, $J = 8.2$ Hz, 2H), 6.85 (s, 1H), 5.12 (s, 1H), 4.52 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 160.1, 159.6, 158.5, 147.7, 142.5, 132.1, 130.5, 129.6, 129.5, 126.5, 121.0, 117.3, 116.0, 115.7, 115.1, 114.5, 103.6, 58.3, 55.5, 37.8; LRMS (EI): *m*/*e* 346 (M^+, 16), 252 (17), 251 (100), 208 (15), 84 (11), 55 (13), 42 (14), 41 (10); Anal. Calcd for $C_{21}H_{15}FN_2O_2$: C, 72.82; H, 4.37; N, 8.09. Found: C, 72.82; H, 4.45; N, 8.08; the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 17.64$ min, $t_{minor} = 21.22$ min.

4.1.7. 3-Amino-1-*p*-tolyl-1*H*-benzo[*f*]chromene-2-carbonitrile 4g.[12a] White solid. Mp 253–254 °C; $[\alpha]_D^{24.3} = -20.3$ (*c* 0.59, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2H), 7.71–7.68 (m, 1H); 7.40–7.37 (m, 2H); 7.25 (d, $J = 8.6$ Hz, 1H), 7.12–7.02 (m, 4H), 5.21 (s, 1H), 4.57 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 8.42$ min, $t_{minor} = 12.28$ min.

4.1.8. 3-Amino-1-(4-nitrophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4h.[3c] Pale yellow solid. Mp 185–186 °C; $[\alpha]_D^{27.4} = -115.9$ (*c* 0.40, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, $J = 9.7$ Hz, 2H), 7.88–7.82 (m, 2H), 7.55–7.51 (m, 1H), 7.45–7.26 (m, 5H), 5.36 (s, 1H), 4.76 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 14.75$ min, $t_{minor} = 20.71$ min.

4.1.9. 3-Amino-1-(4-methoxyphenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4i.[12a] Pale white solid. Mp 194 °C; $[\alpha]_D^{27.1} = -19.5$ (*c* 0.65, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.6$ Hz, 2H), 7.69–7.66 (m, 1H), 7.39–7.36 (m, 2H), 7.22 (d, $J = 10$ Hz, 1H), 7.09 (d, $J = 7.6$ Hz, 2H), 6.78 (d, $J = 7.5$ Hz, 2H), 5.19 (s, 1H), 4.60 (s, 2H), 3.72 (s, 3H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 9.83$ min, $t_{minor} = 16.12$ min.

4.1.10. 3-Amino-1-(2,4-dichlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4j.[12a] White solid. Mp 239–240 °C; $[\alpha]_D^{26.8} = +4.3$ (*c* 0.73, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.61–7.58 (m, 1H), 7.45–7.36 (m, 3H), 7.26–7.24 (m, 1H), 7.03 (dd, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 9.5$ Hz, 1H), 5.84 (s, 1H), 4.67 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 12.90$ min, $t_{minor} = 18.49$ min.

4.1.11. 3-Amino-1-(3-fluorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4k.[12b] White solid. Mp 278–279 °C; $[\alpha]_D^{27.5} = -21.7$ (*c* 0.62, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.82 (d, $J = 8.8$ Hz, 2H), 7.66–7.63 (m, 1H), 7.43–7.40 (m, 2H), 7.28–7.25 (m, 2H), 7.06 (d, $J = 7.7$ Hz, 1H), 6.91–6.84 (m, 1H), 6.79 (d, $J = 9.8$ Hz, 1H) 5.25 (s, 1H), 4.64 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 14.63$ min, $t_{minor} = 20.19$ min.

4.1.12. 3-Amino-1-(3-methoxyphenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4l. White solid. Mp 262–263 °C; $[\alpha]_D^{27.3} = -6.6$ (*c* 0.77, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98–7.85 (m, 3H), 7.45–7.42 (m, 2H), 7.33 (d, $J = 9.0$ Hz, 1H), 7.17 (t, $J = 7.8$ Hz, 1H), 7.0 (s, 2H), 6.78–6.68 (m, 3H), 5.28 (s, 1H), 3.58 (s, 3H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 14.75$ min, $t_{minor} = 21.04$ min.

4.1.13. 3-Amino-1-(2-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4m.[12a] White solid. Mp 265–267 °C; $[\alpha]_D^{23.9} = +28.5$ (*c* 0.48, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.67 (d, $J = 7.7$ Hz, 1H); 7.45–7.37 (m, 3H); 7.26–7.24 (m, 1H), 7.12–7.02 (m, 2H), 6.91 (dd, $J = 8.8$ Hz, 1H), 5.89 (s, 1H), 4.54 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 15.08$ min, $t_{minor} = 23.16$ min.

4.1.14. 3-Amino-1-(3-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4n.[12c] White solid. Mp 240–241 °C; $[\alpha]_D^{25.0} = -18.4$ (*c* 0.62, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 8.6$ Hz, 2H), 7.65–7.62 (m, 1H), 7.43–7.40 (m, 2H), 7.23–7.08 (m, 5H), 5.22 (s, 1H), 4.64 (s, 2H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 14.90$ min, $t_{minor} = 19.62$ min.

4.1.15. 3-Amino-1-(furan-2-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 4o.[3e] White solid. Mp 225–226 °C; $[\alpha]_D^{27.3} = -45.5$ (*c* 0.41, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.5$ Hz, 1H), 7.91 (d, $J = 8.9$ Hz, 2H), 7.54–7.42 (m, 3H), 7.27 (d, $J = 9.2$ Hz, 1H), 7.08 (s, 2H), 6.30–6.22 (m, 2H), 5.48 (s, 1H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 3:2, hexane/2-propanol, 0.7 mL/min); $t_{major} = 14.67$ min, $t_{minor} = 7.71$ min.

4.1.16. 3-Amino-1-pentyl-1*H*-benzo[*f*]chromene-2-carbonitrile 4p.[12d] Colourless oil. $[\alpha]_D^{27.8} = +5.5$ (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91–7.81 (m, 2H), 7.71 (d, $J = 8.6$ Hz, 1H), 7.59–7.44 (m, 2H), 7.14 (d, $J = 9.2$ Hz, 1H), 4.68 (s, 2H), 4.25 (t, $J = 8.7$ Hz, 1H), 1.82–1.79 (m, 2H), 1.46–1.21 (m, 6H), 0.83–0.79 (t, $J = 6.1$ Hz, 3H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 19:1, hexane/2-propanol, 0.7 mL/min); $t_{major} = 30.60$ min, $t_{minor} = 33.27$ min.

4.1.17. Ethyl 3-amino-1-(4-chlorophenyl)-1*H*-benzo[*f*]chromene-2-carboxylate 4q.[12a] White solid. Mp 190–191 °C; $[\alpha]_D^{12.7} = +2.5$ (*c* 0.33, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J = 8.7$ Hz, 1H), 7.76 (t, $J = 8.4$ Hz, 2H), 7.47–7.35 (m, 2H), 7.27–7.25 (m, 3H), 7.13 (d, $J = 7.1$ Hz, 2H), 6.31 (s, 2H), 5.56 (s, 1H), 4.21(q, $J = 5.1$ Hz, 2H), 1.36 (t, $J = 5.9$ Hz, 3H); the enantiomeric ratio was determined by HPLC analysis, using a Chiracel OJ column (25 °C, 254 nm, 9:1, hexane/2-propanol, 0.7 mL/min); $t_{major} = 29.05$ min, $t_{minor} = 35.80$ min.

4.1.18. General procedure for one-pot condensation of malononitrile with an aldehyde and 2-naphthol. To a solution of 0.2 mmol of 2-naphthol, 0.2 mmol of malononitrile and 0.2 mmol of an aldehyde in the presence of 20 mol % of **1c** in 1.0 mL of DCM at room temperature, 30 mg of 4 Å MS was added. Stirring at room temperature was continued for 6–48 h. The crude mixture was purified by column chromatography on silica gel to afford the corresponding products.

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8. When (*Z* or *E*)-ethyl 3-(4-chlorophenyl)-2-cyanoacrylate was tested in this reaction, only a moderate yield (46%) was obtained with a poor enantioselectivity (34% ee, the characterizing data for the corresponding product **4q** was given in Section 4); further optimization of this study with these types of substrates is currently in progress.
9. When phenol was used, no desired product was obtained.
10. CCDC 673964 for **7a** contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.
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