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Organocatalyzed Friedel–Craft-type reaction of 2-naphthol with β,γ-unsaturated α-keto ester to form novel optically active naphthopyran derivatives

Xiao-Sheng Wang [b], Chang-Wu Zheng [a], Sheng-Li Zhao [c], Zhuo Chai [a], Gang Zhao [a,*], Gao-Sheng Yang [b,*]

[a] *Laboratory of Modern Synthetic Organic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b] *Anhui Key Laboratory of Functional Molecular Solids, Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China*
[c] *Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, PR China*

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ABSTRACT

A novel bifunctional thiourea–tertiary-amine-catalyzed enantioselective Friedel–Craft-type addition reaction of 2-naphthol with β,γ-unsaturated α-keto ester was developed. Subsequent dehydration of the reaction adducts with a catalytic amount of concentrated H_2SO_4 in a one-pot fashion readily afforded a series of new optically active naphthopyran derivatives with moderate to good yields (up to 91%) and enantioselectivities (up to 90%).

1. Introduction

Naphthopyran derivatives are an important class of compounds with excellent photochromic properties,[1] some of which are also structural motifs present in many biologically active compounds.[2] For instance, some naphthopyran derivatives could have potential applications in biochemical research as photoswitch tag compounds.[1d] Therefore, the synthesis of such compounds has attracted strong interest.[3] Although several methods have been successfully developed for this purpose, the enantioselective synthesis of naphthopyran derivatives has scarcely been reported.[3]

Recently, we have disclosed an efficient bifunctional thiourea-catalyzed addition–cyclization reaction of 2-naphthol with α,α-dicyanoolefins affording the corresponding naphthopyran derivatives in high yields and moderate enantioselectivities.[4] As an extension of this work,[5] we then wondered if other electrophiles, such as β,γ-unsaturated α-keto esters **2**[6] could be used instead of α,α-dicyanoolefins. Compound **2** was also found to be a suitable reaction component in this reaction system to provide a series of novel optically active naphthopyran derivatives with moderate to good yields and enantioselectivities after a simple conversion step. Herein, we report the details of this study (Fig. 1).

2. Results and discussion

As a starting point, the reaction of β,γ-unsaturated α-keto ester **2a** with 2-naphthol was chosen as a model reaction to investigate. The reaction proceeded well at room temperature in toluene with the cinchona alkaloid-derived thiourea catalyst **1a** to furnish a Friedel–Craft-type addition adduct **4a**. Since compound **4a** is in rapid equilibrium with the cyclic hemiketal **5a**,[6i] it was dehydrated with a catalytic amount of concentrated H_2SO_4[3a] in a one-pot fashion after completion of the Friedel–Craft-type addition step, which provided the naphthopyran derivative **6a** in 79% yield (over two steps) and 57% ee (Scheme 1).

Subsequently, we decided to optimize the reaction conditions, and the results were summarized in Table 1. Firstly, a dramatic solvent effect on both the yield and enantioselectivity was observed, and CH_2Cl_2 was found to be the solvent of choice, giving the desired product **6a** in 73% ee and 82% yield (entry 2). Next, a series of thiourea and tertiary amine-based bifunctional catalysts were screened at room temperature in CH_2Cl_2 (entries 7–11). Interestingly, of all the catalysts examined, the (*R*,*R*)-1,2-cyclohexyldiamine-derived catalyst **1c** was again found to exhibit the best catalytic effect as shown in our previous work[4] (entry 8). Changing the trifluoromethyl phenyl group in **1c** to 4-fluorophenyl **1d**, 4-trifluorophenyl **1e**, or cyclohexyl **1f** groups led to inferior chemical yields and enantioselectivities. Further optimization with **1c** revealed that no beneficial effect on the enantioselectivity could be observed when lowering the reaction temperature to −25 °C (entry 12, 76% ee), while a slightly better enantioselectivity was obtained when 20 mol % of **1c** was used (entry 14, 87% ee).

With the optimized reaction conditions in hand, we then examined a range of β,γ-unsaturated α-keto esters and naphthols to explore the generality of this reaction, and the results are summarized in Table 2. Firstly, several β,γ-unsaturated α-keto esters **2a**–**e** bearing different R^3 substituents were tested in the reaction (Table 2, entries 1–5). It was found that variation of the R^3 groups had a greater influence on the chemical yield of the reaction than on the enantioselectivity. Next, a series of α-keto esters with

* Corresponding authors. Fax: +86 21 64166128.
E-mail addresses: zhaog@mail.sioc.ac.cn (G. Zhao), gshyang@mail.ahnu.edu.cn (G.-S. Yang).

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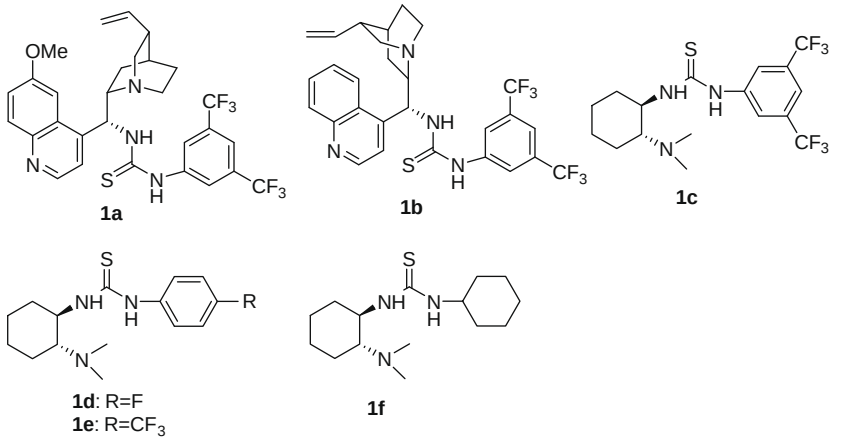
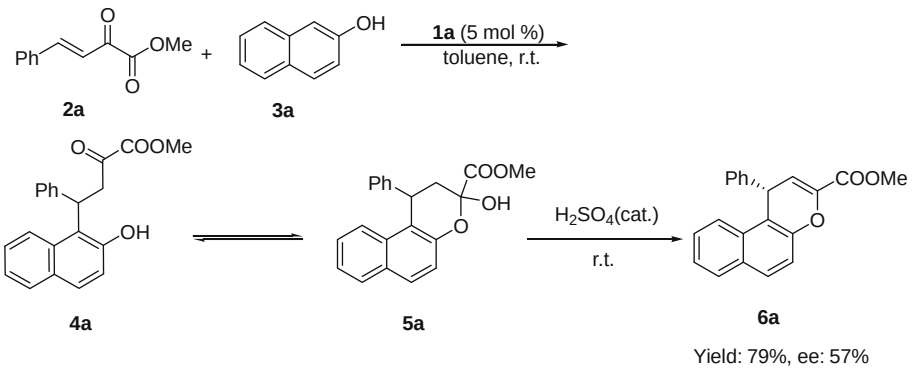


Figure 1. Thiourea–tertiary amine catalysts used in the study.



Scheme 1. The one-pot two-step enantioselective synthesis of **6a**.

differently substituted phenyl rings having the same R^3 = Me were also examined (Table 2, entries 6–13). It seems that the electronic nature of the substituents on the phenyl ring has a dramatic effect on this reaction. With the exception of the *ortho*-Br-substituted substrate **2l** (Table 2, entry 12), substrates bearing *para*- or *meta*-electron-withdrawing groups on the phenyl ring provided much better results than those bearing electron-donating groups in terms of both yield and enantioselectivity. Moreover, two substituted 2-naphthols were also reacted with ketoester **2a** to study the influence of the structure of the naphthol component on the reaction (Table 2, entries 14 and 15). In both cases, comparable enantioselectivities to those of the unsubstituted 2-naphthol were obtained, albeit with lower yields. The absolute configuration of the product **6n** was determined to have an (*S*)-configuration by X-ray crystallographic analysis (Fig. 2).[7]

3. Conclusions

In conclusion, we have reported the enantioselective synthesis of a series of novel naphthopyran derivatives based on an asymmetric Friedel–Craft-type addition reaction of 2-naphthol with β,γ-unsaturated α-keto ester catalyzed by bifunctional thiourea–tertiary amines. With this procedure, the desired naphthopyran derivatives **6** could be obtained with moderate to good yields and enantioselectivities (51–91% yield and 57–90% ee) under mild conditions.

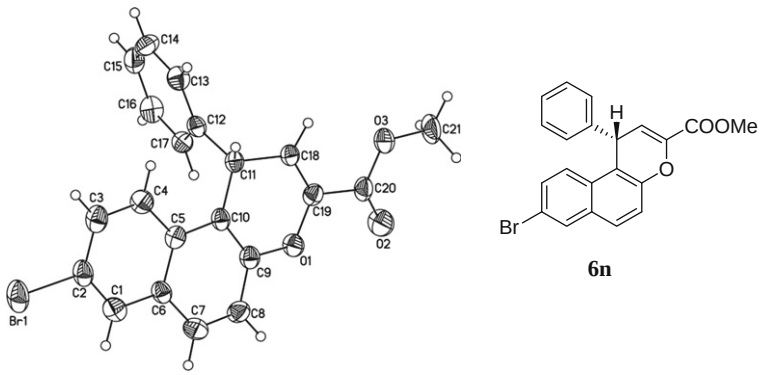


Figure 2. X-ray structure of compound **6n**.

4. Experimental

4.1. General

Unless otherwise indicated, chemicals and solvents were purchased from commercial suppliers and 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 ^{1}H 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, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, and m = multiplet) and coupling constants (Hz), integration. ^{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 and were/are uncorrected. Optical rotations were measured on a JASCO P-1030 Polarimeter at λ = 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).

4.1.1. General procedure for the asymmetric synthesis of naphthopyran derivatives 6a–6o

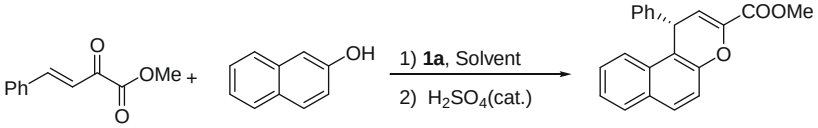
A solution of 0.1 mmol of 2-naphthol, 0.1 mmol of β,γ-unsaturated α-keto ester, and 0.02 mmol of **1c** in 1.0 mL of DCM was stirred at room temperature for 6–48 h (monitored by TLC). Then a drop of concentrated H_2SO_4 (98%) was added directly and stirring was continued for 30 min at room temperature. The crude reaction mixture was directly purified by column chromatography on silica gel to afford the corresponding products.

4.1.1.1. (*S*)-Methyl 4-(2-hydroxynaphthalen-1-yl)-2-oxo-4-phenylbutanoate 4a. White solid. Mp 127–128 °C; IR (KBr): 3476, 3432, 1752, 1729, 1622, 1589, 1451, 1433, 1263, 1224, 1178, 1141, 1060, 812, 750, 760, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79–7.71 (m, 2H), 7.38–7.09 (m, 9H), 4.83–4.72 (m, 1H), 4.19 (s, 0.60H), 3.98 (s, 0.40H), 3.87 (s, 1.18H), 3.82 (s, 1.82H), 2.93–2.86 (m, 0.37H), 2.66–2.53 (m, 1.63H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 150.3, 149.9, 145.7, 143.9, 132.4, 132.1, 130.3, 129.8, 129.3, 129.2, 128.8, 128.4, 128.3, 128.234, 128.197, 127.6, 126.5, 126.3, 125.7, 125.2, 123.7, 123.4, 119.0, 118.9, 116.0, 114.0, 94.6, 93.9, 53.4, 39.9, 36.6, 35.7, 35.0; LRMS (EI): *m*/*e* 231 (M$^+$, 100), 257 (81), 77 (65), 44 (64), 131 (64), 103 (64), 51 (63), 239 (62). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.05; H, 5.41.

4.1.1.2. Methyl 1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6a. White solid. Mp 176–177 °C; $[\alpha]_D^{22} = -341.6$ (*c* 0.50, $CHCl_3$); IR (KBr): 1725, 1674, 1622, 1599, 1516, 1434, 1335, 1262, 1231, 1190, 1113, 1070, 1037, 764, 748, 705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.66–7.64 (m, 1H), 7.42–7.35 (m, 3H), 7.29–7.17 (m, 5H), 6.46 (d, *J* = 4.8 Hz, 1H), 5.35 (d, *J* = 4.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 148.9, 144.3, 138.9, 131.3, 131.2, 129.4, 128.9, 128.4, 127.7, 126.8, 126.7, 124.4, 123.5, 117.9, 114.9, 113.0, 52.3, 39.0; LRMS (EI): *m*/*e* 239 (M$^+$, 100), 257 (65), 315 (44), 240 (19), 258 (13), 317 (10), 226 (7), 316 (7). Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.69; H, 5.22. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 14.24 min, t_{minor} = 17.79 min.

4.1.1.3. (*S*)-Ethyl 1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6b. White solid. Mp 155–156 °C; $[\alpha]_D^{20} = 290.5$ (*c* 0.50, $CHCl_3$); IR (KBr): 1719, 1672, 1597, 1516, 1400, 1371, 1331, 1264, 1228, 1108, 1073, 820, 763, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.66–7.64 (m, 1H), 7.42–7.17 (m, 8H), 6.45 (d, *J* = 4.8 Hz, 1H), 5.35 (d, *J* = 4.8 Hz, 1H), 4.31 (q, *J* = 6.5 Hz, 2H), 1.34 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 149.0, 144.4, 139.1, 131.3, 131.2, 129.3, 128.9, 128.4, 127.8, 126.8, 126.7, 124.4, 123.5, 118.0, 114.6, 113.1, 61.5, 39.0, 14.1; LRMS (EI): *m*/*e* 253 (M$^+$, 100), 257 (86), 225 (59), 330 (39), 226

Table 1
Screen of the optimal reaction conditions for the reaction of **2a** and **3a**[a]



2a **3a** **6a**

Entry	Solvent	Catalyst	Yield[b] (%)	ee[c] (%)
1	Toulene	**1a**	79	57
2	CH_2Cl_2	**1a**	82	73
3	*n*-Hexane	**1a**	66	42
4	CH_2ClCH_2Cl	**1a**	63	35
5	Et_2O	**1a**	47	30
6	MeOH	**1a**	60	8
7	CH_2Cl_2	**1b**	70	66
8	CH_2Cl_2	**1c**	83	80
9	CH_2Cl_2	**1d**	82	72
10	CH_2Cl_2	**1e**	71	75
11	CH_2Cl_2	**1f**	63	37
12[d]	CH_2Cl_2	**1c**	73	76
13[e]	CH_2Cl_2	**1c**	84	83
14[f]	CH_2Cl_2	**1c**	84	87

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **2a** and 0.1 mmol of **3a** in the presence of 5 mol % of **1** in 1.0 mL of solvent at room temperature.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral OD-H column.
[d] The reaction was conducted at −25 °C.
[e] 10 mol % of **1c** was used.
[f] 20 mol % of **1c** was used.

(21), 258 (20), 152 (20), 254 (18). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.79; H, 5.58. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 13.04 min, t_{minor} = 15.07 min.

4.1.1.4. (*S*)-Isopropyl 1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6c. White solid. Mp 111–112 °C; $[\alpha]_D^{21} = -182.9$ (*c* 0.50, $CHCl_3$); IR (KBr): 1723, 1666, 1621, 1599, 1516, 1488, 1264, 1252, 1190, 1127, 1104, 821, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.55 (s, 1H), 7.35–7.16 (m, 8H), 6.33 (d, *J* = 4.8 Hz, 1H), 5.26 (d, *J* = 4.8 Hz, 1H), 5.10–5.07 (m, 1H), 1.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 149.1, 144.5, 139.4, 131.3, 131.2, 129.3, 128.9, 128.4, 127.8, 126.8, 126.6, 124.3, 123.5, 118.1, 114.3, 113.1, 69.3, 39.1, 21.73, 21.70; LRMS (EI): *m*/*e* 225 (M^+, 100), 257 (90), 267 (50), 344 (33), 226 (28), 258 (18), 152 (18), 228 (13). Anal. Calcd for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.27; H, 5.95. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 10.27 min, t_{minor} = 11.60 min.

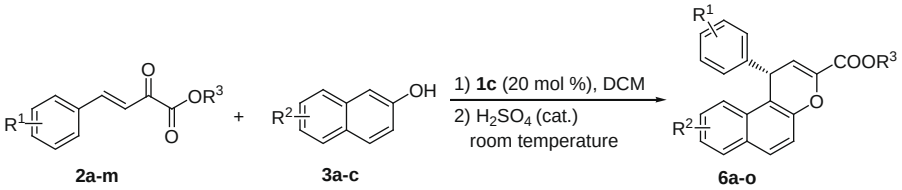
4.1.1.5. (*S*)-Allyl 1-phenyl-1*H*-benzo[f]chromene-3-carboxylate 6d. White solid. Mp 107–108 °C; $[\alpha]_D^{22} = 112.2$ (*c* 0.50, $CHCl_3$); IR (KBr): 1732, 1668, 1621, 1598, 1512, 1302, 1260, 1249, 1120, 808, 759, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.66–7.63 (m, 1H), 7.41–7.17 (m, 8H); 6.47 (d, *J* = 5.1 Hz, 1H), 6.04–5.91 (m, 1H), 5.40–5.26 (m, 3H), 3.81–4.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 149.0, 144.3, 138.9, 131.6, 131.3, 131.2, 129.3, 128.9, 128.4, 127.7, 126.8, 126.7, 124.4, 123.5, 119.0, 117.9, 115.0, 113.0, 66.0, 39.0; LRMS (EI): *m*/*e* 265 (M^+, 100), 257 (75), 342 (34), 225 (28), 152 (21), 266 (20), 258 (16), 69 (16). Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.67; H, 5.23. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 13.25 min, t_{minor} = 16.11 min.

4.1.1.6. (*S*)-Benzyl 1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6e. White solid. Mp 136–137 °C; $[\alpha]_D^{22} = 147.4$ (*c* 0.50, $CHCl_3$); IR (KBr): 1732, 1668, 1622, 1598, 1515, 1454, 1330, 1261, 1185, 1119, 820, 747, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.40–7.62 (m, 1H), 7.39–7.34 (m, 8H); 7.25–7.16 (m, 5H), 6.47 (d, *J* = 4.8 Hz, 1H), 5.34 (d, *J* = 12.2 Hz, 2H), 5.20 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 149.0, 144.3, 139.0, 135.3, 131.3, 131.2, 129.4, 129.0, 128.6, 128.5, 128.4, 127.8, 126.9, 126.7, 124.4, 123.5, 118.0, 115.1, 113.1, 67.1, 39.1; LRMS (EI): *m*/*e* 315 (M^+, 100), 257 (89), 69 (56), 91 (55), 57 (54), 392 (43), 55 (42), 97 (39). Anal. Calcd for $C_{27}H_{20}O_3$: C, 82.63; H, 5.14. Found: C, 82.65; H, 5.13. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 11.61 min, t_{minor} = 12.76 min.

4.1.1.7. (*S*)-Methyl 1-(4-bromophenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6f. White solid. Mp 141–142 °C; $[\alpha]_D^{22} = -350.9$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–7.79 (m, 2H), 7.59–7.56 (m, 1H), 7.41–7.35 (m, 5H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 148.9, 143.3, 139.1, 132.1, 131.2, 131.0, 129.6, 129.4, 128.5, 126.8, 124.5, 123.3, 120.8, 117.9, 114.1, 112.4, 52.4, 38.4; LRMS (EI): *m*/*e* 239 (M^+, 100), 335 (32), 337 (30), 240 (17), 394 (15), 396 (13), 152 (13), 226 (11). Anal. Calcd for $C_{21}H_{15}BrO_3$: C, 63.81; H, 3.83. Found: C, 63.85; H, 3.96. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 14.45 min, t_{minor} = 18.06 min.

4.1.1.8. (*S*)-Methyl 1-(4-chlorophenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6g. White solid. Mp 143–144 °C; $[\alpha]_D^{22} = -369.7$ (*c* 0.50, $CHCl_3$); IR (KBr): 1737, 1673, 1448, 1436, 1263, 1252, 1121, 821, 765, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.81–7.78 (m, 2H), 7.59–7.56 (m, 1H), 7.41–7.35 (m, 3H), 7.26–7.22 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.42 (d, *J* = 5.4 Hz, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 148.9, 143.3,

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



2a-m **3a-c** **6a-o**

Entry	2	R^1	R^2	R^3	Product	Yield[b] (%)	ee[c] (%)
1	**2a**	H	H **3a**	Me	**6a**	84	87
2	**2b**	H	H **3a**	Et	**6b**	91	82
3	**2c**	H	H **3a**	*i*Pr	**6c**	64	84
4	**2d**	H	H **3a**	Allyl	**6d**	61	84
5	**2e**	H	H **3a**	Bn	**6e**	51	78
6	**2f**	4-Br	H **3a**	Me	**6f**	91	87
7	**2g**	4-Cl	H **3a**	Me	**6g**	89	87
8	**2h**	4-F	H **3a**	Me	**6h**	75	86
9	**2i**	4-OEt	H **3a**	Me	**6i**	58	72
10	**2j**	4-NO_2	H **3a**	Me	**6j**	78	90
11	**2k**	3-Cl	H **3a**	Me	**6k**	71	86
12	**2l**	2-Br	H **3a**	Me	**6l**	52	57
13	**2m**	1,5-Di(OMe)	H **3a**	Me	**6m**	58	60
14	**2a**	H	6-Br **3b**	Me	**6n**	57	86
15	**2a**	H	7-OCH_3 **3c**	Me	**6o**	68	82

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **2a** and 0.1 mmol of **3a** in the presence of 20 mol % of **1** in 1.0 mL of CH_2Cl_2 at room temperature.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral OD-H or OD column. The absolute configuration of product **6n** was determined to be (*S*)-configuration by X-ray crystallographic analysis, while the others **6a–m, 6o** were assigned by assuming that a similar catalytic mechanism was taken.

139.1, 132.1, 131.2, 131.0, 129.6, 129.4, 128.5, 126.8, 124.5, 123.3, 120.8, 117.9, 114.1, 112.4, 52.4, 38.4; LRMS (EI): *m*/*e* 239 (M^+, 100), 291 (52), 350 (25), 57 (20), 240 (17), 293 (17), 69 (16), 71 (16). Anal. Calcd for $C_{21}H_{15}ClO_3$: C, 71.90; H, 4.31. Found: C, 71.91; H, 4.33. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 14.06 min, t_{minor} = 17.52 min.

4.1.1.9. (*S*)-Methyl 1-(4-ethoxyphenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6i. White solid. Mp 155–156 °C; $[\alpha]_D^{22}$ = −278.6 (*c* 0.50, $CHCl_3$); IR (KBr): 1735, 1672, 1607, 1597, 1508, 1339, 1301, 1252, 1228, 1116, 816, 752, 588, 522 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.66 (s, 1H), 7.40–7.36 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.78 (d, *J* = 7.9 Hz, 2H), 6.45 (d, *J* = 4.5 Hz, 1H), 5.29 (d, *J* = 4.5 Hz, 1H), 3.95–3.80 (m, 2H), 3.85 (s, 3H), 1.35 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 157.7, 148.8, 138.7, 136.4, 131.3, 131.2, 129.2, 128.7, 128.4, 126.6, 124.4, 123.5, 117.9, 115.2, 114.8, 113.3, 63.3, 52.3, 38.1, 14.7; LRMS (EI): *m*/*e* 301 (M^+, 100), 239 (35), 302 (24), 273 (13), 152 (8), 360 (7), 168 (6), 240 (5). Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.65; H, 5.62. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 15.64 min, t_{minor} = 17.23 min.

4.1.1.10. (*S*)-Methyl 1-(4-nitrophenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6j. White solid. Mp 156–157 °C; $[\alpha]_D^{22}$ = −417.2 (*c* 0.50, $CHCl_3$); IR (KBr): 1738, 1675, 1596, 1518, 1349, 1301, 1263, 1253, 1123, 848, 821, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.0 Hz, 2H), 7.85–7.82 (m, 2H), 7.49–7.35 (m, 6H); 6.40 (d, *J* = 5.2 Hz, 1H), 5.48 (d, *J* = 5.2 Hz, 1H), 3.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 151.2, 148.9, 146.7, 139.8, 131.3, 130.8, 130.0, 128.7, 128.5, 127.1, 124.8, 124.3, 122.9, 117.9, 112.9, 111.6, 52.5, 38.8; LRMS (EI): *m*/*e* 239 (M^+, 100), 361 (19), 302 (18), 240 (17), 152 (9), 226 (7), 168 (7), 256 (6). Anal. Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.89; H, 4.38; N, 3.73. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 31.23 min, t_{minor} = 44.24 min.

4.1.1.11. (*S*)-Methyl 1-(3-chlorophenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6k. White solid. Mp 218–219 °C; $[\alpha]_D^{23}$ = −341.0 (*c* 0.34, $CHCl_3$); IR (KBr): 1734, 1724, 1677, 1598, 1436, 1337, 1264, 1233, 1117, 1037, 815, 764, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.41–7.38 (m, 3H); 7.19–7.07 (m, 4H), 6.42 (d, *J* = 4.5 Hz, 1H), 5.32 (d, *J* = 4.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 148.9, 146.2, 139.2, 134.8, 131.2, 131.0, 130.2, 129.7, 128.5, 127.8, 127.1, 126.9, 125.8, 124.6, 123.2, 117.9, 114.0, 112.2, 52.4, 38.7; LRMS (EI): *m*/*e* 57 (M^+, 100), 69 (87), 55 (85), 97 (79), 239 (71), 71 (70), 83 (70), 95 (66). Anal. Calcd for $C_{21}H_{15}ClO_3$: C, 71.90; H, 4.31. Found: C, 71.76; H, 4.41. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 15.52 min, t_{minor} = 18.66 min.

4.1.1.12. (*R*)-Methyl 1-(2-bromophenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6l. White solid. Mp 203–204 °C; $[\alpha]_D^{23}$ = −102.3 (*c* 0.50, $CHCl_3$); IR (KBr): 1727, 1676, 1622, 1599, 1465, 1434, 1336, 1263, 1234, 1120, 1120, 821, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–7.80 (m, 2H), 7.61 (d, *J* = 3.3 Hz, 1H), 7.42–7.38 (m, 4H); 7.04 (s, 2H), 6.78–6.76 (m, 1H), 6.52 (d, *J* = 3.6 Hz, 1H), 5.84 (d, *J* = 3.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 149.4, 142.7, 139.6, 132.7, 131.2, 131.0, 130.7, 129.6, 128.4, 127.0, 124.6, 123.3, 122.0, 117.7, 112.6, 112.5, 52.4, 38.1; LRMS (EI): *m*/*e* 239 (M^+, 100), 240 (17), 335 (16), 337 (16), 396 (13), 394 (13), 226 (13), 113 (12). Anal. Calcd for $C_{21}H_{15}BrO_3$: C, 63.81; H, 3.83. Found: C, 63.98; H, 3.98. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 11.94 min, t_{minor} = 14.10 min.

4.1.1.13. (*S*)-Methyl 1-(2,5-dimethoxyphenyl)-1*H*-benzo[*f*]chromene-3-carboxylate 6m. White solid. Mp 203–204 °C; $[\alpha]_D^{21}$ = −241.4 (*c* 0.50, $CHCl_3$); IR (KBr): 1729, 1669, 1598, 1500, 1442, 1257, 1243, 1210, 1182, 1125, 1105, 808, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.57–7.55 (m, 1H), 7.39–7.35 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 4.8 Hz, 1H), 6.28 (s, 1H), 5.79 (d, *J* = 4.8 Hz, 1H), 3.99 (s, 3H), 3.84 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 154.0, 149.5, 149.4, 139.5, 133.3, 131.3, 131.1, 129.1, 128.2, 126.7, 124.4, 123.3, 117.8, 116.3, 114.2, 113.0, 111.7, 111.0, 56.0, 55.3, 52.2, 31.7; LRMS (EI): *m*/*e* 57 (M^+, 100), 55 (94), 97 (89), 69 (86), 83 (77), 95 (74), 71 (70), 81 (67). Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 72.72; H, 5.23. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 14.63 min, t_{minor} = 16.58 min.

4.1.1.14. (*S*)-Methyl 8-bromo-1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6n. White solid. Mp 224–225 °C; $[\alpha]_D^{23}$ = −273.1 (*c* 0.50, $CHCl_3$); IR (KBr): 1722, 1676, 1590, 1501, 1433, 1335, 1267, 1235, 1118, 762, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.43–7.38 (m, 2H), 7.29–7.16 (m, 5H), 6.45 (d, *J* = 4.8 Hz, 1H), 5.31 (d, *J* = 4.8 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 149.0, 143.9, 138.8, 132.4, 130.3, 129.9, 129.8, 129.0, 128.4, 127.6, 127.0, 125.2, 119.1, 118.3, 114.7, 113.3, 52.4, 38.9; LRMS (EI): *m*/*e* 319 (M^+, 100), 317 (100), 335 (50), 337 (49), 396 (32), 394 (31), 226 (23), 151 (23). Anal. Calcd for $C_{21}H_{15}BrO_3$: C, 63.81; H, 3.83. Found: C, 63.84; H, 4.03. The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 13.34 min, t_{minor} = 16.87 min.

4.1.1.15. (*S*)-Methyl 9-methoxy-1-phenyl-1*H*-benzo[*f*]chromene-3-carboxylate 6o. White solid. Mp 193–194 °C; $[\alpha]_D^{23}$ = −325.5 (*c* 0.50, $CHCl_3$); IR (KBr): 1737, 1668, 1621, 1513, 1254, 1221, 1205, 1123, 834, 757, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 10.1 Hz, 2H), 7.27–7.18 (m, 6H), 6.98 (dd, *J* = 2.0, 8.6 Hz, 1H), 6.89 (s, 1H), 6.44 (d, *J* = 5.1 Hz, 1H), 5.24 (d, *J* = 5.1 Hz, 1H), 3.85 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 158.1, 149.4, 144.3, 138.8, 132.6, 129.8, 129.0, 128.9, 127.8, 126.9, 126.4, 116.4, 115.3, 114.7, 112.1, 103.1, 54.9, 52.3, 39.4; LRMS (EI): *m*/*e* 269 (M^+, 100), 287 (44), 346 (30), 270 (19), 226 (16), 288 (11), 69 (9), 55 (8). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.25; H, 5.04; The enantiomeric ratio was determined by HPLC analysis, using a Chiracel OD-H column (25 °C, 254 nm, 9:1, hexane/2-propanol, 1.0 mL/min); t_{major} = 13.27 min, t_{minor} = 17.50 min.

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7. CCDC 699716 contains the supplementary crystallographic data for **6b**. These data can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.