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Enantioselective synthesis of multifunctionalized 4*H*-pyran derivatives using bifunctional thiourea-tertiary amine catalysts

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ABSTRACT

A series of novel chiral multifunctionalized 4*H*-pyran derivatives were easily accessed via the one-pot asymmetric Michael addition-cyclization reaction between malononitrile and β,γ-unsaturated α-keto esters catalyzed by chiral bifunctional thiourea-tertiary amine catalysts. With the optimized reaction conditions, the desired products were obtained with 50–68% yields and 72–88% ees.

1. Introduction

Multifunctionalized 4*H*-pyrans are important structural units present in many natural or synthetic compounds with important biological or pharmacological activities such as anti-coagulant, anticancer, spasmolytic, and anti-anaphylactic activities.[1–3] In addition, some of these compounds could serve as useful intermediates for organic synthesis.[4] Therefore, numerous efforts have been devoted to the synthesis of these compounds.[5] However, to the best of our knowledge, catalytic enantioselective syntheses of these types of compounds have rarely been reported.

Being interested in the utilization of β,γ-unsaturated α-keto esters as useful reaction components in organic synthesis,[6] we have realized the enantioselective synthesis of naphthopyran derivatives[7] using bifunctional chiral thiourea-tertiary-amine catalysts.[8] As a continuation of our efforts in this field, we report herein the preparation of some thiourea-tertiary-amine catalysts and their applications to the asymmetric Michael addition–cyclization reaction of malononitrile with β,γ-unsaturated α-keto ester leading to the synthesis of a series of chiral 4*H*-pyran derivatives.

2. Results and discussion

Firstly, the reaction of β,γ-unsaturated α-keto ester **2a** with malononitrile was chosen as a model reaction to optimize the reaction conditions and the results are summarized in Table 1. The use of Takemoto's catalyst **1a**[8c] gave the desired product **4a** in 39% yield and 71% ee, along with some unidentifiable byproducts (Table 1, entry 1). Encouraged by this result, we then synthesized another three known catalysts **1b**–**1d**[9] structurally related to **1a** for further investigation. However, the use of these catalysts failed to improve the result (Table 1, entries 2–4). It is worthy to note the difference between the results of catalysts **1c** and **1d**, which underscored the importance of the match of stereocontrol elements in catalysts. Then another two known thiourea-tertiary-amine catalysts of different chiral architecture were also examined. The quinine-derived catalyst **1e**[9] gave the desired product in 32% ee (Table 1, entry 5) while the phenylalanine-derived catalyst **1f**[9] 60% ee (Table 1, entry 6). In view of the fact that amino acids are inexpensive, easily available, and ready for modular modification, we then synthesized four new catalysts **1g**–**1j** based on **1f**. For catalysts **1g** and **1h** with changes on the tertiary amine moiety, only slightly higher ees were obtained compared with **1f** (Table 1, entries 7 and 8). A sharp drop in the ee value was observed in the instance of catalyst **1i** in which an adamantyl group was installed instead of the 3,5-bis(trifluoromethyl)phenyl group in **1f** (Table 1, entry 9). In addition, the C_2-symmetric catalyst **1j** with two tertiary amine moieties also provided rather poor results (Table 1, entry 10). In light of the above results, further optimization efforts were carried out with catalyst **1a**. The use of several other solvents such as $CHCl_3$, CH_3CN, THF, and MeOH all led to inferior results (Table 1, entries 11–14). Increasing the loading of the catalyst to 10 mol % gave only a little improvement in the enantioselectivity, while reducing the loading of the catalyst to 2 mol % deteriorated the enantioselectivity remarkably (Table 1, entries 15 and 16). A reduction in the ee value was also observed when the concentration of the substrates was doubled (Table 1, entry 17).[10] To our delight, lowering the reaction temperature to −30 °C improved both the yield and ee significantly (Table 1, entry 18). However, further lowering of the reaction temperature to −78 °C gave no apparent improvement, yet with a largely prolonged reaction time (Table 1, entry 19) (see Fig. 1).

With the optimized reaction conditions in hand (Table 1, entry 18), we then explored the generality of this reaction with a spectrum of

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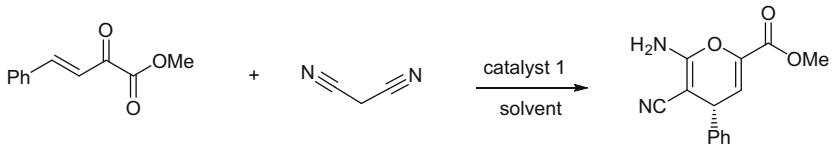
Table 1
Screen of the optimal reaction conditions for the reaction of **5a** and **6**[a]



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

Entry	Solvent	Catalyst	Yield[b] (%)	ee[c] (%)
1	Toluene	**1a**	39	71
2	Toluene	**1b**	39	56
3	Toluene	**1c**	39	40
4	Toluene	**1d**	38	0
5	Toluene	**1e**	38	32
6	Toluene	**1f**	40	60
7	Toluene	**1g**	39	61
8	Toluene	**1h**	40	64
9	Toluene	**1i**	39	26
10	Toluene	**1j**	39	8
11	$CHCl_3$	**1a**	39	58
12	CH_3CN	**1a**	38	23
13	THF	**1a**	41	34
14	MeOH	**1a**	33	7
15[d]	Toluene	**1a**	39	72
16[e]	Toluene	**1a**	35	40
17[f]	Toluene	**1a**	40	48
18[g]	Toluene	**1a**	64	78
19[h]	Toluene	**1a**	65	80

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **2a** and 0.11 mmol of **3** in the presence of 5 mol % of **1** in 2.0 mL of solvent at room temperature under nitrogen atmosphere, 4 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral OD column.
[d] 10 mol % of **1a** was used.
[e] 2 mol % of **1a** was used.
[f] 1.0 mL of toluene was used.
[g] The reaction was conducted at −30 °C, 14 h.
[h] The reaction was conducted at −78 °C, 36 h.

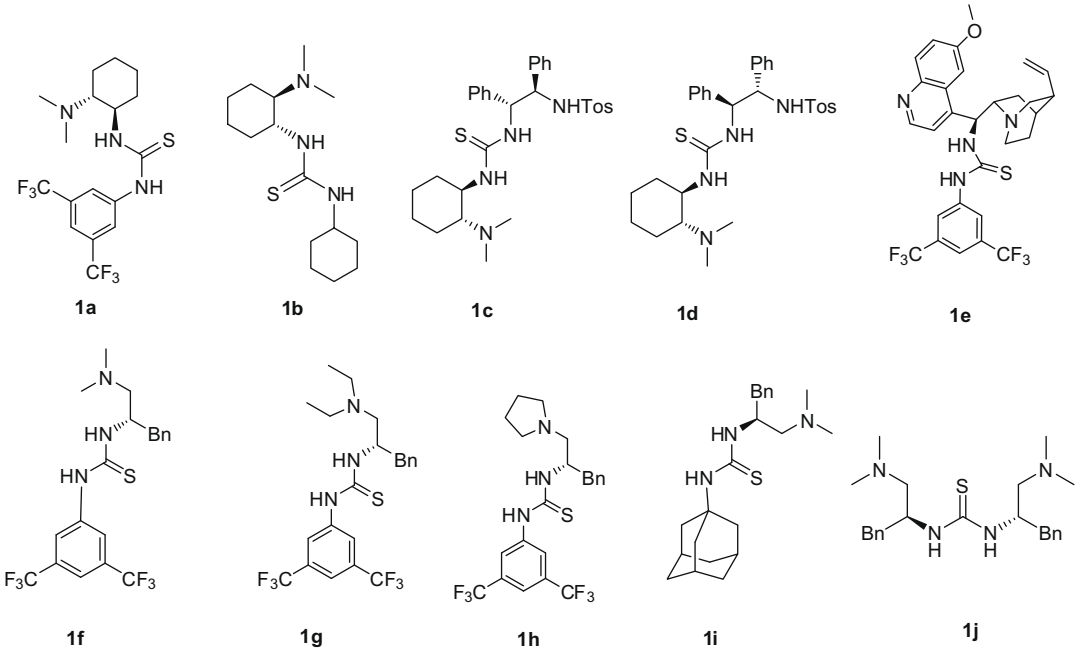
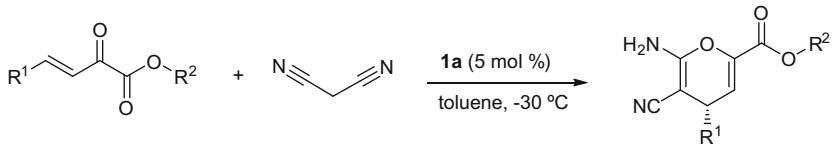


Figure 1. Thiourea-tertiary amine catalysts used in the study.

β,γ-unsaturated α-keto esters and the results are summarized in Table 2. Firstly, several β,γ-unsaturated α-keto esters **2a–i** bearing different R^1 substituents were tested (Table 2, entries 1–9). Except for substrate **2f** with a nitro group on the phenyl group, variation of R^1 brought little influence on the yields and the enantioselectivities, irrespective of the electronic nature, bulk or positions of the substituents on the phenyl ring. Substrates with different R^2 substituents on the ester moiety were also studied in the reaction (Table 2, entries 10–13).

Table 2
Enantioselective synthesis of 4*H*-pyran derivatives catalyzed by **1a**[a]



2 **3** **4**

Entry	2	R^1	R^2	Product	Yield[b] (%)	ee[c] (%)
1	**2a**	Ph	Me	**4a**	64	78
2	**2b**	4-FC_6H_4	Me	**4b**	66	81
3	**2c**	4-ClC_6H_4	Me	**4c**	64	82
4	**2d**	4-BrC_6H_4	Me	**4d**	68	88
5	**2e**	2,4-diClC_6H_3	Me	**4e**	62	88
6	**2f**	4-$NO_2C_6H_4$	Me	**4f**	50	72
7	**2g**	4-$EtOC_6H_4$	Me	**4g**	61	85
8	**2h**	2-BrC_6H_4	Me	**4h**	65	83
9	**2i**	2,5-di$MeOC_6H_3$	Me	**4i**	65	80
10	**2j**	Ph	Bn	**4j**	63	80
11	**2k**	Ph	4-BrBn	**4k**	58	80
12	**2l**	Ph	*i*-Pr	**4l**	57	75
13	**2m**	Ph	Allyl	**4m**	60	77

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **2a–m** and 0.11 mmol of **3** in the presence of 5 mol % of **1a** in 2.0 mL of toluene at −30 °C for 12 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis on a chiral OD or AD column. The absolute configuration of **4d** was determined to be *R* configuration by X-ray crystallographic analysis.

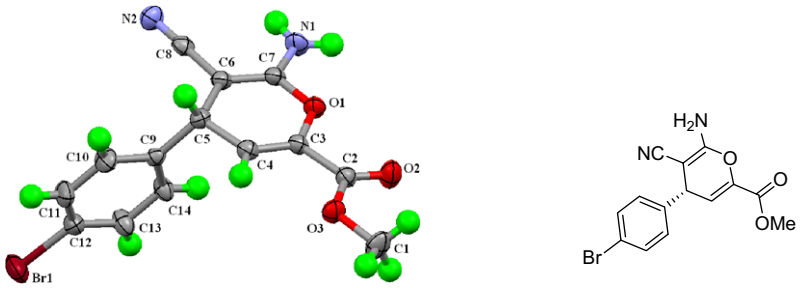


Figure 2. X-ray structure of compound **4d**.

Similarly, no significant difference in yields and enantioselectivities were observed with these substrates (entries 10–13). The absolute configuration of the product **4d** was determined to be (*R*)- by X-ray crystallographic analysis (Fig. 2).[11]

3. Conclusions

In conclusion, we have developed a simple and novel method for the enantioselective synthesis of a series of 4*H*-pyran derivatives through the one-pot asymmetric addition-cyclization of malononitrile to β,γ-unsaturated α-keto ester catalyzed by bifunctional thiourea-tertiary amines. The desired products could be obtained with moderate yields and good enantioselectivities (50–68% yields and 72–88% ees).

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 (300–400 mesh). 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, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a DPX-300 (100 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 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. Mass spectra analyses were performed on API 200 LC/MS system (Applied Biosystems Co. Ltd).

4.2. Preparation of catalysts 1g–1j

Catalysts **1a**[8c], **1b**[9a], **1c**[9e], **1d**[9e], **1e**[9a], **and 1f**[9d] were synthesized according to the literature.

4.2.1. (*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-(diethylamino)-3-phenylpropan -2-yl)thiourea 1g

This compound was prepared according to a known procedure from (*S*)-N^1,N^1-diethyl-3-phenylpropane-1,2-diamine[12] and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene as a pale yellow oil. Yield: 66%; $[\alpha]_D^{22.1} = -32.5$ (*c* 1.60, $CHCl_3$); IR (neat)

ν = 3236, 2974, 1607, 1495, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.59 (s, 1H), 7.21–7.38 (m, 5H), 6.76 (br s, 1H), 4.03 (br s, 1H), 3.01–3.05 (m, 1H), 2.62–2.80 (m, 5H), 2.46–2.57 (m, 2H), 0.94–0.99 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 141.8, 136.3, 131.6 (J = 29.2 Hz), 129.0, 127.3, 123.3, 123.0 (J = 207.8 Hz), 117.7, 59.6, 57.0, 47.4, 39.7, 14.1, 10.7; LRMS (EI): *m/e* 58 (7.76), 86 (100), 91 (6.52), 271 (19.49), 477 (M^+, 0.74); HRMS (EI): 477.1676; Calcd for $C_{22}H_{25}F_6N_3S$: 477.1673.

4.2.2. (*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-phenyl-3-(pyrrolidin-1-yl)prop- an-2-yl) thiourea 1h

This compound was prepared according to a known procedure from (*S*)-1-phenyl-3-(pyrrolidin-1-yl)propan-2-amine[10c] and 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene as a white solid. Yield: 68%; Mp 60–62 °C; $[\alpha]_D^{22.1} = -23.8$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3550, 2972, 2880, 1615, 1540, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.59 (s, 1H), 7.28–7.39 (m, 3H), 7.22 (d, J = 6.9 Hz, 1H), 6.39 (br s, 1H), 4.01 (br s, 1H), 2.96–3.05 (m, 2H), 2.74–2.82 (m, 3H), 2.50–2.63 (m, 3H), 1.81 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 142.4, 137.4, 136.5, 132.0 (J = 32.1 Hz), 129.2, 127.6, 124.8, 123.3 (J = 228.5 Hz), 117.9, 62.5, 56.8, 54.3, 40.0, 23.9; LRMS (EI): *m/e* 55 (4.55), 84 (100), 271 (7.84), 475 (M^+, 0.32); HRMS (EI): 475.1515; Calcd for $C_{22}H_{23}F_6N_3S$: 475.1517.

4.2.3. 1-Adamantan-1-yl-3((*S*)-1-benzyl-2-dimethylamino-ethyl)-thiourea 1i

This compound was prepared according to a known procedure[9d] from 1-adamantanamine and ((*S*)-2-isothiocyanato-3-phenylpropyl)-dimethylamine[13] as a white solid. Yield: 58%; Mp 59–61 °C; $[\alpha]_D^{22.1} = -12.9$ (*c* 1.00, $CDCl_3$); IR (KBr) ν = 3550, 2972, 2880, 1615, 1540, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.33 (m, 5H), 6.06 (s, 1H), 4.11 (m, 1H), 3.16–3.17 (m, 1H), 2.81–2.89 (m, 1H), 2.42–2.49 (m, 1H), 2.27–2.32 (m, 1H), 2.18 (s, 6H), 2.04–2.08 (m, 9H), 1.65–1.69 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 138.6, 129.7, 128.7, 126.6, 53.9, 45.4, 41.9, 36.4, 29.6; LRMS (EI): *m/e* 58 (100), 91 (8.76), 135 (7.63), 161 (11.80), 371 (M^+, 0.19); HRMS (EI): 371.2388; Calcd for $C_{22}H_{33}N_3S$: 371.2395.

4.2.4. 1-((*R*)-1-(Dimethylamino)-3-phenylpropan-2-yl)-3-((*S*)-1-(dimethylamino)-3-phenylpropan-2-yl)thiourea 1j

This compound was prepared according to a known procedure[9d] from (*S*)-N^1,N^1-dimethyl-3-phenylpropane-1,2-diamine and ((*S*)-2-isothiocyanato-3-phenyl propyl)-dimethylamine[13] as a colorless oil. Yield: 53%; $[\alpha]_D^{22.1} = -18.5$ (*c* 1.00, $CHCl_3$); IR (neat) ν = 3550, 2972, 2880, 1615, 1540, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17–7.33 (m, 10H), 2.88 (s, 4H), 2.08–2.42 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 136.6, 128.6, 127.4, 125.6, 61.3, 53.2, 44.2, 37.9; LRMS (EI): *m/e* 58 (100), 91 (36.61), 161 (92.81), 238 (47.32), 398 (M^+, 2.03); HRMS (EI): 398.2507; Calcd for $C_{23}H_{34}N_4S$: 398.2504.

4.3. General procedure for the asymmetric synthesis of 4*H*-pyran derivatives 4a–4m

To a solution of β,γ-unsaturated α-keto ester (0.1 mmol) and malononitrile (0.11 mmol) in 2.0 mL of toluene, **1a** (0.005 mmol) was added. The mixture was sealed and stirred at −30 °C for the time indicated in Table 2 (monitored by TLC). Then the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (hexane/acetate = 5:1) to afford the corresponding products.

4.3.1. (*R*)-Methyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate 4a

White solid. yield: 64%. Mp 171–173 °C; $[\alpha]_D^{22.1} = -105.6$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3437, 2197, 1740, 1683, 1644, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 6.30 (d, J = 4.2 Hz, 1H), 4.68 (s, 2H), 4.32 (d, J = 4.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 159.1, 141.8, 138.2, 128.9, 127.8, 127.7, 119.1, 115.6, 58.8, 52.6, 38.5, 30.8; LRMS (EI): *m/e* 77 (23.6), 119 (32.0), 131 (31.7), 179 (100), 197 (65.0), 256 (M^+, 41); HRMS (EI): 256.0854; Calcd for $C_{14}H_{12}N_2O_3$: 256.0848. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 49.6 min, t_{minor} = 52.7 min.

4.3.2. (*R*)-Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-4*H*-pyran-2-carboxylate 4b

White solid; yield: 66%. Mp 180–183 °C; $[\alpha]_D^{22.1} = -68.1$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3439, 3297, 2191, 1740, 1678, 1634, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, 2H), 7.06 (t, 2H), 6.26 (d, J = 4.1 Hz, 1H), 4.68 (s, 2H), 4.31 (d, J = 4.1 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (J = 245.7 Hz), 160.3, 138.6, 137.9, 129.6 (J = 8.2 Hz), 119.2, 116.3, 115.5, 59.2, 52.2, 38.1, 31.2; LRMS (EI): *m/e* 101 (49.76), 149 (100), 179 (85.79), 215 (98.5), 274 (M^+, 45.3); HRMS (EI): 274.0760; Calcd for $C_{14}H_{11}FN_2O_3$: 274.0754. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 50.7 min, t_{minor} = 46.6 min.

4.3.3. (*R*)-Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-4*H*-pyran-2-carboxylate 4c

White solid; yield: 64%. Mp 210–212 °C; $[\alpha]_D^{22.1} = -132.4$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3449, 3296, 2194, 1739, 1680, 1640, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 6.9 Hz, 2H), 7.19 (d, J = 6.9 Hz, 2H), 6.25 (d, J = 3.9 Hz, 1H), 4.70 (s, 1H), 4.30 (d, J = 3.9 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.4, 140.5, 138.7, 134.0, 129.5, 129.5, 119.1, 115,2, 58.8, 53.0, 38.3, 31.2; LRMS (EI): *m/e* 119 (42.25), 165 (32), 179 (100), 231 (72.61), 290 (M^+, 24.95); HRMS (EI): 290.0458; Calcd for $C_{14}H_{11}ClN_2O_3$: 290.0465. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 55.7 - min, t_{minor} = 48.8 min.

4.3.4. (*R*)-Methyl 5-Amino-3-(4-bromophenyl)-4-cyanocyclohexa-1,4-dienecarboxylate 4d

White solid; yield: 68%. Mp 172–174 °C; $[\alpha]_D^{22.1} = -50.7$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3449, 3296, 2194, 1739, 1680, 1640, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 6.24 (d, J = 4.5 Hz, 1H), 4.72 (s, 2H), 4.29 (d, J = 4.3 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.1, 160.7, 159.3, 141.1, 138.3, 132.9, 132.4, 130.6, 122.2, 115.1, 111.2, 58.9, 53.0, 38.3, 29.9; LRMS (EI): *m/e* 102 (76.37), 119 (36.99), 179 (100), 209 (44.88), 275 (46.98), 334 (M^+, 25.51); HRMS (EI): 333.9950; Calcd for $C_{14}H_{11}BrN_2O_3$: 333.9953. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 56.6 min, t_{minor} = 49.5 min.

4.3.5. (*S*)-Methyl 6-amino-5-cyano-4-(2,4-dichlorophenyl)-4*H*-pyran-2-carboxylate 4e

White solid. yield: 62%. Mp 165–168 °C; $[\alpha]_D^{22.1} = -189.5$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3461, 3429, 2190, 1745, 1683, 1642, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17(s, 1H), 7.29–7.30 (m, 2H), 6.28 (d, J = 4.5 Hz, 1H), 4.85–4.86 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 160.3, 138.8, 137.2, 134.3, 133.5, 130.8, 129.7, 128.1, 118.7, 113.6, 56.5, 52.8, 35.0, 30.0; LRMS (EI): *m/e* 119 (25.97), 136 (23.90), 179 (100), 199 (58.57), 265 (43.44), 324 (M^+, 23.89); HRMS (EI): 324.0059; Calcd for $C_{14}H_{10}Cl_2N_2O_3$: 324.0068. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 54.3 min, t_{minor} = 48.2 min.

4.3.6. (*R*)-Methyl 6-amino-5-cyano-4-(4-nitrophenyl)-4*H*-pyran-2-carboxylate 4f

Yellow solid; yield: 50%. Mp 223–225 °C; $[\alpha]_D^{22.1} = -10.3$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3438, 3200, 2194, 1736, 1681, 1648, 1589 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9 Hz, 2H), 7.44 (d, *J* = 9 Hz, 2H), 6.26 (d, *J* = 4.2 Hz, 1H), 4.79 (s, 2H), 4.45 (d, *J* = 4.3 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.2, 160.2, 150.4, 147.4, 139.1, 129.1, 123.9, 118.4, 113.8, 55.8, 52.0, 38.5; LRMS (EI): *m/e* 119 (33.28), 179 (100), 196 (11.70), 242 (57.59), 301 (M^+, 38.95); HRMS (EI): 301.0697; Calcd for $C_{14}H_{11}N_3O_5$: 301.0699. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 64.0 min, t_{minor} = 58.3 min.

4.3.7. (*R*)-Methyl6-amino-5-cyano-4-(4-ethoxyphenyl)-4*H*-pyran-2-carboxylate 4g

White solid; yield: 61%. Mp 137–139 °C; $[\alpha]_D^{22.1} = -96.1$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3437, 3299, 2195, 1739, 1679, 1640, 1599, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.27 (d, *J* = 4.8 Hz, 1H), 4.65 (s, 2H), 4.25 (d, *J* = 4.8 Hz, 1H), 4.01 (q, 2H), 3.82 (s, 3H), 1.41 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 159.3, 138.3, 134.3, 129.0, 119.5, 116.1, 115.2, 63.7, 59.4, 52.9, 38.0, 15.0; LRMS (EI): *m/e* 119 (80.74), 179 (95.42), 241 (100), 300 (M^+, 97.25); HRMS (EI): 300.1112; Calcd for $C_{16}H_{16}N_2O_4$: 300.1110. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 61.7 - min, t_{minor} = 48.1 min.

4.3.8. (*S*)-Methyl 6-amino-4-(2-bromophenyl)-5-cyano-4*H*-pyran-2-carboxylate 4h

White solid; yield: 65%. Mp 181–183 °C; $[\alpha]_D^{22.1} = -173.5$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3467, 3340, 2194, 1729, 1686, 1644, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 1H), 7.27–7.39 (m, 2H), 7.16 (t, 1H), 6.33 (d, *J* = 4.8 Hz, 1H), 4.92 (s, 2H), 4.89 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.5, 140.4, 138.7, 133.5, 130.4, 129.6, 128.7, 123.3, 119.1, 114.6, 57.2, 53.0, 38.1; LRMS (EI): *m/e* 102 (50.57), 130 (33.91), 179 (100), 255 (51.98), 334 (M^+, 11.78); HRMS (EI): 333.9965; Calcd for $C_{14}H_{11}BrN_2O_3$: 333.9953. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 51.1 - min, t_{minor} = 68.7 min.

4.3.9. (*S*)-Methyl 6-amino-5-cyano-4-(2,5-dimethoxyphenyl)-4*H*-pyran-2-carboxylate 4i

White solid; yield: 65%. Mp 133–135 °C; $[\alpha]_D^{22.1} = -153.8$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3310, 3002, 2958, 2184, 1740, 1661, 1503, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.19 (m, 2H), 6.73 (d, *J* = 5.4 Hz, 1H) 5.17 (d, *J* = 5.4 Hz, 1H), 5.14 (s, 2H), 4.23(s, 3H), 4.22 (s, 3H), 4.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 160.4, 154.3, 151.0, 138.6, 131.0, 112.0, 115.9, 115.8, 112.9, 111.9, 57.4, 56.3, 56.0, 52.8, 32.1; LRMS (EI): *m/e* 158 (100), 191 (69.04), 289 (69.75), 316 (M^+, 89.06); HRMS (EI): 316.1056; Calcd for $C_{16}H_{16}N_2O_5$: 316.1059. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 62.3 - min, t_{minor} = 50.0 min.

4.3.10. (*R*)-Benzyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate 4j

White solid. yield: 63%. Mp 140–142 °C; $[\alpha]_D^{22.1} = -55.6$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3437, 3407, 3326, 2186, 1741, 1676, 1636, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.36 (m, 10H), 6.30 (d, *J* = 4.5 Hz, 1H), 5.24 (q, 2H),4.73 (s, 2H), 4.29 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.1, 141.8, 138.3, 134.8, 129.0, 128.7, 127.9, 127.8, 119.1, 115.8, 67.6, 59.0, 38.6, 30.9; LRMS (EI): *m/e* 66 (27.16), 77 (29.19), 91 (100), 131 (14.47), 197 (29.53), 255 (24.04), 332 (M^+, 10.13); HRMS (EI): 332.1169; Calcd for $C_{20}H_{16}N_2O_3$: 332.1161. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel AD column (25 °C, 254 nm, 4:1, hexane/2-propanol, 0.5 mL/min); t_{major} = 47.8 min, t_{minor} = 38.5 min.

4.3.11. (*R*)-4-Bromobenzyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate 4k

White solid; yield: 58%. Mp 137–139 °C; $[\alpha]_D^{22.1} = -50.1$ (*c* 1.00, $CHCl_3$); IR (KBr) ν = 3440, 3392, 3315, 2189, 1732, 1677, 1599, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.51 (m, 9H), 6.30 (d, *J* = 4.5 Hz, 1H), 5.22 (q, 2H), 4.67 (s, 2H), 4.31 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.4, 142.0, 138.4, 134.0, 132.1, 1305, 128.0, 123.1, 119.3, 116.3, 67.0, 59.2, 38.9, 30.6; LRMS (EI): *m/e* 90 (38.62), 131 (18.39), 171 (100), 197 (77.84), 335 (17.14), 411 (M^+, 7.18); HRMS (EI): 410.0268; Calcd for $C_{20}H_{15}BrN_2O_3$: 410.0266. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 4:1, hexane/2-propanol, 0.5 mL/min); t_{major} = 56.6 min, t_{minor} = 48.4 min.

4.3.12. (*R*)-Isopropyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate 4l

White solid; yield: 57%. Mp 198–200 °C; $[\alpha]_D^{22.1} = -63.0$ (*c* 1.00, $CDCl_3$); IR (KBr) ν = 3447, 3333, 2193, 1722, 1678, 1637, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.38 (m, 5H), 6.25 (d, *J* = 4.5 Hz, 1H), 5.13 (m, 1H), 4.71 (s, 2H), 4.30 (d, *J* = 4.8 Hz, 1H), 1.26–1.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.5, 142.3, 138.9, 129.3, 128.1, 119.5, 115.2, 59.2, 38.9, 31.2, 21.9; LRMS (EI): *m/e* 131 (62.43), 165 (90.73), 197 (100), 284 (M^+, 41.95); HRMS (EI): 284.1167; Calcd for $C_{16}H_{16}N_2O_3$: 284.1161. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel OD column (25 °C, 254 nm, 1:4, hexane/2-propanol, 0.1 mL/min); t_{major} = 59.7 min, t_{minor} = 49.7 min.

4.3.13. (*R*)-Allyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate 4m

White solid; yield: 60%. Mp 156–158 °C; $[\alpha]_D^{22.1} = -99.5$ (*c* 1.00, $CDCl_3$); IR (KBr) ν = 3438, 3317, 2199, 1741, 1682, 1646, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.40 (m, 5H), 6.31 (d, *J* = 4.2 Hz, 1H), 5.87–5.99 (m, 1H), 5.27–5.38 (m, 2H), 4.70–4.73 (m, 4H), 4.31 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.2, 141.9, 138.3, 131.2, 129.1, 127.9, 127.8, 119.5, 119.2, 115.7, 66.4, 58.8, 38.6, 29.7; LRMS (EI): *m/e* 131 (58.52), 197 (100), 205 (82.99), 282 (M^+, 44.34); HRMS (EI): 282.1000; Calcd for $C_{16}H_{14}N_2O_3$: 282.1004. The enantiomeric ratio was determined by HPLC analysis, using a Chiralcel AD column (25 °C, 254 nm, 4:1, hexane/2-propanol, 0.5 mL/min); t_{major} = 33.0 min, t_{minor} = 24.8 min.

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11. CCDC-716175 contains the supplementary crystallographic data for **4d**. These data can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.
12. This compound was prepared according to Ref. 10c. Characterizing data: colorless oil; $[\alpha]_D^{22.1} = +44.2$ (*c* 2.00, $CDCl_3$); IR (film) $\nu = 3373, 2968, 2931, 1602, 1495\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H), 3.37 (s, 2H), 3.11–3.37 (m, 1H), 2.37–2.79 (m, 8H), 0.99 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 129.2, 128.5, 126.3, 58.8, 50.8, 47.4, 41.0, 11.8; LRMS (EI): *m/e* 58 (9.72), 72 (11.70),86 (100), 91 (7.88), 206 (M^+, 0.56); HRMS (EI): 206.1779; Calcd for $C_{13}H_{22}N_2$: 206.1783.
13. This compound was prepared according to Ref. 10b. Characterizing data: white solid; M.p. 86–88 °C; $[\alpha]_D^{22.1} = -47.0$ (*c* 1.50, $CDCl_3$); IR (KBr) $\nu = 3085, 3062, 2100, 1603, 1535, 1454\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5H), 3.91–3.40 (m, 1H), 2.97–3.03 (m, 1H), 2.81–2.88 (m, 1H), 2.50–2.57 (m, 1H), 2.41–2.47 (m, 1H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 131.9, 128.5, 127.6, 126.1, 62.2, 57.3, 44.8, 38.9; LRMS (EI): *m/e* 42 (7.76), 58 (100), 91 (9.55), 129 (24.43), 220 (M^+, 4.93); HRMS (EI): 220.1034; Calcd for $C_{12}H_{16}N_2S$: 220.1036.