Efficient kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives catalyzed by Takemoto's organocatalyst†

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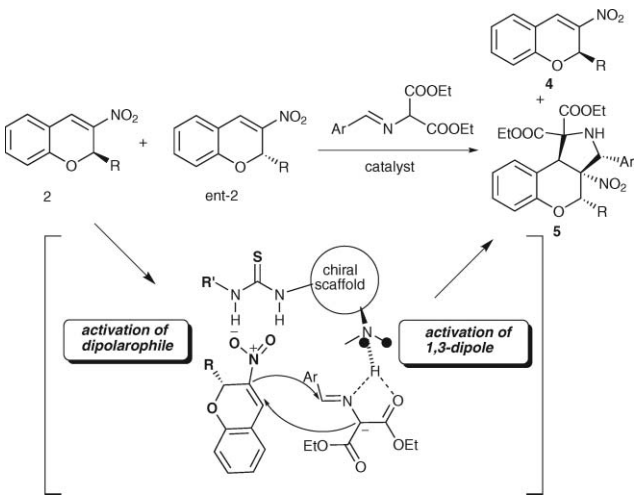
Efficient kinetic resolution of racemic 3-nitro-2*H*-chromenes by bifunctional thiourea afforded optically active (*R*)-3-nitro-2*H*-chromene derivatives with moderate to good enantioselectivities, which simultaneously gave the multifunctional 3,4-diphenyl-3a-nitrobenzopyrano-[3,4-*c*]-pyrrolidine-1,1-dicarboxylate derivatives with four vicinal chiral carbon centers.

Introduction

The chiral chroman unit is the core structure in a number of natural products.[1] Many chiral chroman derivatives are known to exhibit a wide range of biological properties,[2] for example anticancer, diuretic, anticoagulant, and anti-anaphylactic activity.[3] Particularly, many chiral chroman units are also the most significant member of the vitamin E family serving as a natural lipophilic antioxidant and radical scavenger.[4] Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds.[5,6] Among this class of compounds, 3-nitro-2*H*-chromenes are very important units, which are recognized due to their biological activity and their importance as precursors of flavonols, amines, and other important targets.[7] Recently, Xu's group and Sankararaman's group reported the enantioselective tandem oxa-Michael–Henry reaction of salicylaldehyde derivatives to nitroolefins for chiral 3-nitro-2*H*-chromene derivatives catalyzed by a chiral amine.[8] Unfortunately, low ees were observed for a range of substrates, and in general over 96 h were required in order to achieve good yields at room temperature. In addition, although 3-nitro-chromene derivatives as 2p components in 1,3-dipolar cycloadditions of azomethine ylides has been reported,[9] to the best of our knowledge, there is no report on the direct catalytic asymmetric 1,3-dipolar cycloaddition of 2-aryl-3-nitrochromenes with azomethine ylides. These encouraged us to explore a more general and versatile synthetic methodologies to this class of compounds. Besides chiral pool strategies (use of enantiopure starting materials provided by nature) and enantioselective synthesis (preparation from achiral precursors using chiral reagents or catalysts),[10] the kinetic resolution of racemates has always played a central role in the preparation of optically active compounds.[11,12] Recently, thiourea–tertiary amines were investigated and established as effective bifunctional organocatalysts in asymmetric catalysis[13] and many exciting discoveries have been made in the thiourea–tertiary amine catalyzed reactions, such as Michael additions, aza-Henry reactions, domino reactions and dynamic kinetic resolution (DKR).[12] Motivated by our success in the thiourea-catalyzed asymmetric formal [3+2] cycloaddition of azomethine ylides with nitroolefins to provide highly functionalized pyrrolidines with high diastereo- and enantioselectivities.[14] We hoped that the bifunctional thiourea catalysts **1a–1d**, which proved to be highly effective in the Michael addition,[12] would effect a kinetic resolution (KR) of racemic 3-nitro-2*H*-chromene derivatives. If the selectivity of the catalyst is sufficiently high, a KR process will be of practical significance, for both the remaining **4** and the converted substrate enantiomers **5** have a wide range of potential applications in pharmaceutical chemistry (Scheme 1). Herein, we set out to expand this methodology to synthesis of chiral 3-nitro-2*H*-chromene derivatives by kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives. Notably, the kinetic resolution gave the 3-nitro-2*H*-chromene derivatives with good enantioselectives, which simultaneously gave the multifunctional diethyl 3,4-diphenyl-3a-nitro-benzopyrano[3,4-*c*] pyrrolidine-1,1-dicarboxylate derivatives with four vicinal chiral carbon centers for the first time.



Scheme 1 Kinetic resolution of 3-nitro-2*H*-chromene derivatives **2** *via* [3+2] cycloaddition catalyzed by thiourea–tertiary amine bifunctional organocatalysts.

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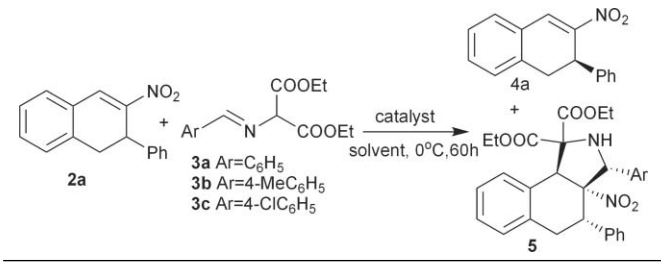
Table 1 Optimization of the reaction conditions[a]

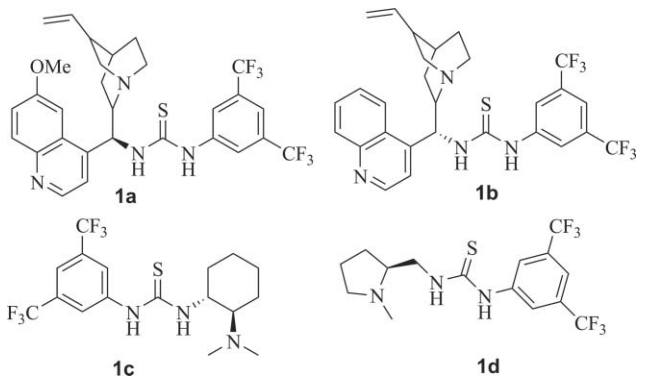


Entry	Catalyst	Solvent	Ee (%)[b]/yield (%)[c] **4**	Ee (%)[b]/yield (%)[c] **5**[d]
1	**1a**	DCM	29/42	1/40
2	**1b**	DCM	42/41	9/35
3	**1c**	DCM	65/46	13/11
4	**1d**	DCM	37/40	21/49
5	**1c**	Toluene	87/41	19/25
6	**1c**	THF	51/53	7/40
7	**1c**	Ethanol	15/31	0/62
8[e]	**1c**	Toluene	81/43	25/25
9[f]	**1c**	Toluene	78/46	31/28

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.1 mmol of **3a**, 10 mol% catalyst, in 1 mL solvent at 0 °C. [b] Determined by chiral HPLC analysis. [c] Isolated yield. [d] The diastereoselectivities (>99 : 1) were determined after isolation. [e] Reaction with **3b**. [f] Reaction with **3c**.

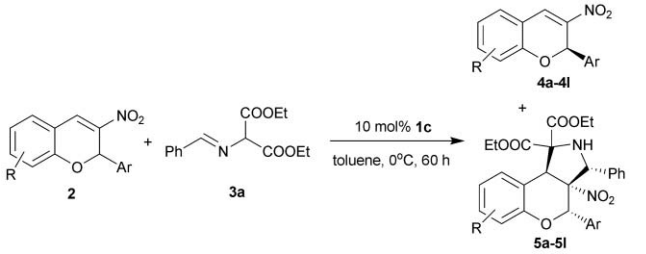
Results and discussion

Our studies began with the identification of the best catalyst and reaction conditions for this kinetic resolution using racemic 3-nitro-2*H*-chromene **2a** as a model substrate (Table 1). We first investigated the catalytic activity of thiourea for the [3+2] cycloaddition of 3-nitro-2*H*-chromene **2a** with azomethine ylides. We found that the catalysts **1a** and **1b** (Scheme 2), which have been successfully used in the asymmetric Michael reactions,[13e,f] were found to be highly active catalysts at 0 °C. Clean products **4a** and **5** were obtained, while the ees were very low (Table 1, entries 1 and 2). Subsequently, we were pleased to find that Takemoto's catalsyst **1c** exhibited higher catalytic activity, and 41% yield with 65% ee could be obtained under the same conditions (Table 1, entry 3). Low enantioselectivity was obtained using catalyst **1d** derived from L-proline (Table 1, entry 4). In the next stage of the studies, different solvents were screened. The kinetic resolution could be efficiently performed in all solvents tested affording **4a** and **5** but with low enantioselectivity. Gratifyingly, we achieved an good ee (87%) with 43% yield by utilizing the toluene as solvent, under the same conditions. Using other azomethine ylides as the 1,3-dipoles gave a similar enantioselectivity (entries 8 and 9).



Scheme 2 The structure of thiourea catalysts.

Table 2 Asymmetric kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives[a]



Entry	Ar (**2**)		Ee (%)[b]/yield (%)[c] **4**	Ee (%)[b]/yield (%)[c] **5**[d]
1	C_6H_5	**2a**	87/41 **4a**	19/25 **5a**
2	4-ClC_6H_4	**2b**	77/42 **4b**	17/26 **5b**
3	4-BrC_6H_4	**2c**	79/41 **4c**	35/40 **5c**
4	4-$CF_3C_6H_4$	**2d**	85/46 **4d**	49/31 **5d**
5	4-MeC_6H_4	**2e**	82/47 **4e**	45/27 **5e**
6	4-$MeOC_6H_4$	**2f**	68/49 **4f**	21/23 **5f**
7[e]	C_6H_5	**2g**	73/37 **4g**	53/47 **5g**
8[f]	C_6H_5	**2h**	86/43 **4h**	33/29 **5h**
9[f]	4-MeC_6H_4	**2i**	87/45 **4i**	57/35 **5i**
10[f]	4-$MeOC_6H_4$	**2j**	83/47 **4j**	70/36 **5j**
11[f]	4-ClC_6H_4	**2k**	73/45 **4k**	51/41 **5k**
12[f]	4-BrC_6H_4	**2l**	82/39 **4l**	13/32 **5l**

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a–l**, 0.1 mmol of **3a**, 10 mol% **1c**, in 1 mL toluene at 0 °C. [b] Determined by chiral HPLC analysis. [c] Isolated yield. [d] The diastereoselectivities (>99 : 1) were determined after isolation. [e] At –10 °C for 12 h. [f] At –10 °C for 36 h

To test the substrate scope of our kinetic resolution process, the reaction of various 3-nitro-2*H*-chromene derivatives (**2a–2l**) and α-amino malonate imine (**3a**) was studied under the optimized conditions using 10 mol% of Takemoto's catalyst (**1c**) as the catalyst. The results are collected in Table 2.

As shown in Table 2, the kinetic resolution of various 3-nitro-2*H*-chromene derivatives with α-amino malonate imine (**3a**) all gave excellent yields and good enantioselectivities of the desired products **4a–4l** and **5a–5l**. The kinetic resolution of 3-nitro-2*H*-chromene derivatives with electron-withdrawing substituents or electron-donating groups on the Ar group afford the desired products with a slight effect on enantioselectivities (Table 2, entries 2–6, 77–85% ee), except for the substrate **2f** (Table 2, entry 6), for which the product was obtained in moderate enantioselectivity (68% ee). In addition, the electronic nature of a substituent on the aromatic moiety of **2g–2l** (Fig. 1) affects the asymmetric induction of the kinetic resolution. The substrate **2g** with a strong electron-withdrawing substituent (–F) showed high reactivity—the kinetic resolution could proceed smoothly with good ee even at –10 °C in a short time (Table 2, entry 7). On the other hand,

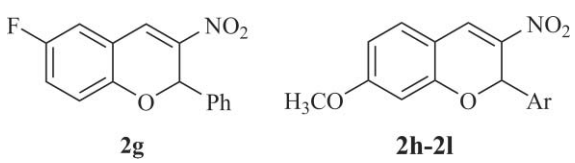


Fig. 1 Structures of the 3-nitro-2*H*-chromene derivatives.

the substrates **2h–2l** with an electron-donating group (–MeO) led to an increase in enantioselectivity (entries 9–12). Notably, the kinetic resolution gave the 3-nitro-2*H*-chromene derivatives with good enantioselectivities, which simultaneously gave the multifunctional diethyl 3,4-diphenyl-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate derivatives **5a–5l** with moderate enantioselectivities (up to 70% ee) possess four vicinal chiral carbon centers. To the best of our knowledge, the chiral multifunctional chroman derivatives **5a–5l** were obtained for the first time.

To determine the absolute configuration of the [3+2] cycloadducts **5**, single crystal suitable for X-ray crystallographic analysis was fortunately obtained from **5c** that bears a bromide atom.‡ As shown in Fig. 2, it is composed of (C7-*S*, C8-*R*, C9-*S*, C22-*R*) configuration.

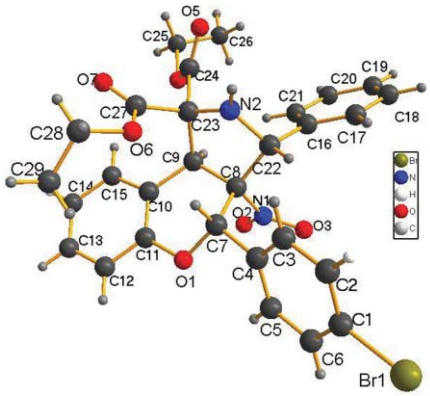


Fig. 2 Molecular structure of enantiopure **5c**.

Conclusions

In conclusion, we have described a novel and practical organocatalytic method for the synthesis of optically active 3-nitro-2*H*-chromene derivatives. To the best of our knowledge, this is the first time that kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives catalyzed by Takemoto's catalyst afford the 3-nitro-2*H*-chromene derivatives with good enantioselectivities. Notably, the kinetic resolution gave the optically active 3-nitro-2*H*-chromene derivatives, which simultaneously gave the multifunctional diethyl 3,4-diphenyl-3a-nitrobenzopyrano [3,4-*c*]-pyrrolidine-1,1-dicarboxylate derivatives **5** with moderate enantioselectivities (up to 70% ee) possessing four vicinal chiral carbon centers. The KR process was of practical significance, for both the 3-nitro-2*H*-chromene derivatives **4** and chroman derivatives **5** have a wide range of potential applications in pharmaceutical chemistry.

‡ Crystal data for **5c** $C_{29}H_{27}BrN_2O_7$ (595.44), Monoclinic, space group $P2_1$, $a = 11.2327(3)$ Å, $b = 10.1083(3)$ Å, $c = 12.0414(3)$ Å, $V = 1333.26(6)$ Å^3, $Z = 2$, specimen $0.25 \times 0.07 \times 0.06$ mm^3, $T = 296(2)$ K, SIEMENS P4 diffractometer, absorption coefficient 1.593 mm^{-1}, reflections collected 20 445, independent reflections 6121 [R(int) = 0.0338], refinement by Full-matrix least-squares on F^2, data/restraints/parameters 6121/1/352, goodness-of-fit on $F^2 = 1.032$, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0378$, w$R_2 = 0.0873$, R indices (all data) $R_1 = 0.0563$, w$R_2 = 0.0935$, largest diff. peak and hole 0.342 and –0.664 e Å^{-3}, Flack = 0.015(6). Crystallographic data for the structure **5c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 752804. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internet.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk]. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b922668k

Experimental

General methods

NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ ($\delta = 7.26$ ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$ ppm) for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. ESI-HRMS spectrometer was measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer. Optical rotations were measured at 589 nm at 25 °C. Enantiomeric excess was determined by HPLC analysis on Chiralpak AD and OJ columns.

General procedure for kinetic resolution racemic 3-nitro-2*H*-chromene derivatives with a chiral thiourea

General procedure: **2a** 25 mg (0.1 mmol), **3a** 20 mg (0.1 mmol), thiourea 4.1 mg (0.01 mmol) were stirred in toluene (1 ml) at –10 °C for 60 h. Then flash chromatography on silica gel (PE : EA=10 : 1) gave **4a** as a pale yellow solid and **5a** as a white solid.

(*R*)-3-Nitro-2-phenyl-2*H*-chromene (4a). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (s, 1H), 7.38-7.22 (m, 7H), 6.98-6.94 (m, 1H), 6.85-6.83 (m, 1H), 6.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.6, 136.8, 134.3, 130.5, 129.5, 129.3, 128.9, 128.9, 128.9, 127.1,127.1, 127.1, 122.6, 118.0, 117.3, 74.3; ESI-HRMS: calcd. for $C_{15}H_{11}NO_3$+H Exact Mass: 254.08216, found 254.08099; $[\alpha]_D^{25} = -33.0$ (c 0.27, ethanol), 87% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AS-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 9.052$ min, $t_{major} = 15.732$ min.

(*R*)-2-(4-Chlorophenyl)-3-nitro-2*H*-chromene (4b). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.34-7.26 (m, 6H), 7.02-6.84 (m, 2H), 6.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3, 135.5, 135.3, 134.5, 130.5, 129.5, 129.1, 128.4, 122.8, 117.8, 117.3, 73.5. IR (KBr) cm^{-1} 1639, 1603, 1499; ESI-HRMS: calcd. for $C_{15}H_{10}ClNO_3$+H 288.04378, found 288.04069; $[\alpha]_D^{25} = -20.0$ (c 0.19, ethanol), 77% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 8.00$ min, $t_{major} = 9.69$ min.

(*R*)-2-(4-Bromophenyl)-3-nitro-2*H*-chromene (4c). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08 (s, 1H), 7.48-7.25 (m, 6H), 7.05-7.02 (m, 1H), 6.90-6.88 (m, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3, 135.8, 134.5, 132.1, 132.1, 130.5, 129.5, 128.7, 128.7, 117.8, 117.3, 73.5; ESI-HRMS: calcd. for $C_{15}H_{10}BrNO_3$ 330.98396, found 330.98215; $[\alpha]_D^{25} = -33.8$ (c 0.34, ethanol), 79% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 9.26$ min, $t_{major} = 10.90$ min.

(*R*)-2-(4-(Trifluoromethyl)phenyl)-3-nitro-2*H*-chromene (4d). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08 (s, 1H), 7.58-7.33 (m, 6H), 7.04-6.88 (m, 2H), 6.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.3, 134.7, 130.7, 129.8, 127.4, 127.4, 126.0, 126.0, 125.9, 125.9, 123.0, 117.7, 117.3, 73.5; ESI-HRMS: calcd. for $C_{16}H_{10}F_3NO_3$+Na 344.05215, found 344.05117; $[\alpha]_D^{25} = -31.0$ (*c* 0.28, ethanol), 85% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 6.57$ min, $t_{major} = 8.40$ min.

(*R*)-3-Nitro-2-*p*-tolyl-2*H*-chromene (4e). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (s, 1H), 7.30-7.24 (m, 4H), 7.10-6.82 (m, 4H), 6.53 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 134.3, 130.4, 129.6, 129.2, 127.0, 122.5, 117.3, 74.1, 21.2; ESI-HRMS: calcd. for $C_{16}H_{14}NO_3$+H 268.09805, found 268.09793; $[\alpha]_D^{25} = -34.5$ (*c* 0.35, ethanol), 82% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 6.59$ min, $t_{major} = 9.56$ min.

(*R*)-2-(4-Methoxyphenyl)-3-nitro-2*H*-chromene (4f). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (s, 1H), 7.32-7.25 (m, 4H), 7.00-6.96 (m, 1H), 6.84-6.80 (m, 3H), 6.52 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 180.5, 134.2, 130.3, 129.1, 128.9, 128.5, 128.5, 122.4, 118.0, 117.3, 114.2, 73.9, 55.3; ESI-HRMS: calcd. for $C_{16}H_{13}NO_4$+Na 307.08317, found 307.08306; $[\alpha]_D^{25} = -20.0$ (*c* 0.22, ethanol), 68% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 12.29$ min, $t_{major} = 19.91$ min.

(*R*)-6-Fluoro-2-phenyl-3-nitro-2*H*-chromene (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (s, 1H), 7.38-7.33 (m, 5H), 7.07-7.01 (m, 2H), 6.86-6.83 (m, 1H), 6.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.9, 136.2, 129.6, 128.9, 128.3, 128.2, 127.0, 120.9, 120.6, 118.6, 118.5, 115.9, 115.7, 74.2; ESI-HRMS: calcd. for $C_{15}H_{10}FNO_3$+H 272.04432, found 272.04419; $[\alpha]_D^{25} = -35.5$ (*c* 0.38, ethanol), 73% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 9.84$ min, $t_{major} = 12.43$ min.

(*R*)-7-Methoxy-2-phenyl-3-nitro-2*H*-chromene (4h). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.39-7.22 (m, 6H), 6.57-6.54 (m, 2H), 6.79 (d, $J = 2.4$ Hz, 1H), 6.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.1, 155.6, 137.9, 131.7, 129.8, 129.3, 128.8, 127.0, 111.1, 109.8, 102.2, 74.5, 55.6; ESI-HRMS: calcd. for $C_{16}H_{13}NO_4$+Na 307.08317, found 307.08303; $[\alpha]_D^{25} = -26.3$ (*c* 0.51, ethanol), 86% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{major} = 15.93$ min, $t_{minor} = 19.65$ min.

(*R*)-7-Methoxy-2-*p*-tolyl-3-nitro-2*H*-chromene (4i). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08 (s, 1H), 7.31-7.15 (m, 5H), 6.60-6.42 (m, 3H), 3.81 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.0, 155.6, 138.4, 134.1, 131.6, 130.0, 127.0, 127.0, 111.0, 109.7, 102.2, 74.4, 56.6, 21.2; ESI-HRMS: calcd. for $C_{17}H_{15}NO_4$+Na 320.09006, found 320.08917; $[\alpha]_D^{25} = -31.8$ (*c* 0.21, ethanol), 87% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{major} = 13.40$ min, $t_{minor} = 15.43$ min.

(*R*)-7-Methoxy-2-(4-methoxyphenyl)-3-nitro-2*H*-chromene (4j). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.32-7.23 (m, 3H), 6.85-6.83 (m, 2H), 6.57-6.38 (m, 3H), 3.79-3.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.1, 131.6, 130.0, 129.2, 128.5, 114.2, 111.2, 109.7, 102.2, 74.3, 55.6, 55.3; ESI-HRMS: calcd. for $C_{17}H_{15}NO_5$+Na 336.08547, found 336.08395; $[\alpha]_D^{25} = -19.7$ (*c* 0.11, ethanol), 83% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{major} = 25.77$ min, $t_{minor} = 28.10$ min.

(*R*)-7-Methoxy-2-(4-chlorophenyl)-3-nitro-2*H*-chromene (4k). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.33-7.23 (m, 5H), 6.60-6.40 (m, 3H), 3.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.2, 155.4, 135.6, 135.3, 131.8, 130.0, 129.1, 129.0, 128.5, 128.5, 128.4, 128.4, 111.0, 111.0, 102.3, 73.8, 56.7; ESI-HRMS: calcd. for $C_{16}H_{12}ClNO_4$+H 317.04609, found 317.04446; $[\alpha]_D^{25} = -37.6$ (*c* 0.27, ethanol), 73% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{major} = 13.81$ min, $t_{minor} = 17.47$ min.

(*R*)-7-Methoxy-2-(4-bromophenyl)-3-nitro-2*H*-chromene (4l). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.05 (s, 1H), 7.47-7.23 (m, 5H), 6.59-6.40 (m, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.3, 136.0, 135.2, 132.0, 131.8, 130.0, 128.7, 110.0, 110.0, 108.4, 102.2, 100.7, 55.7, 55.7; ESI-HRMS: calcd. for $C_{16}H_{12}BrNO_4$+Na 383.98503, found 383.98497; $[\alpha]_D^{25} = -29.0$ (*c* 0.36, ethanol), 82% ee; The enantiomeric ratio was determined by HPLC on Chiralpak OJ-RH column (10% 2-propanol–hexane, 1 mL min^{-1}), $t_{major} = 15.05$ min, $t_{minor} = 19.78$ min.

Diethyl 3-phenyl-4-phenyl-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5a). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, $J = 7.6$ Hz, 1H), 7.34-7.05 (m, 11H), 6.94 (t, $J = 7.6$ Hz, 1H), 6.73 (d, $J = 8.4$ Hz, 1H), 5.68 (s, 1H), 5.64 (s, 1H), 5.55 (d, $J = 9.6$ Hz, 1H), 5.55 (d, $J = 8.4$ Hz, 1H), 4.47-4.42 (m, 2H), 3.73-3.62 (m, 2H), 3.19 (d, $J = 5.2$ Hz, 1H), 1.38 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7, 169.8, 152.0, 136.0, 134.5, 130.0, 129.3, 129.1, 128.9, 128.8, 128.4, 128.3, 127.7, 122.2, 121.6, 118.2, 96.9, 69.0, 62.7, 62.1, 47.6, 14.1; ESI-HRMS: calcd. for $C_{29}H_{28}N_2O_7$+H 517.19873, found 517.19693; $[\alpha]_D^{25} = -22.5$ (*c* 0.70, ethanol), 19% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 9.07$ min, $t_{major} = 14.57$ min.

3-Phenyl-4-(4-chlorophenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5b). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, $J = 7.6$ Hz, 1H), 7.36-7.07 (m, 10H), 6.98-6.94 (m, 1H), 6.74-6.72 (m, 1H), 5.65(s, 1H), 5.61(s,1H), 5.50(s,1H), 4.49-4.39 (m, 2H), 3.77-3.59(m, 2H), 3.17 (s, 1H), 1.38 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6,168.7, 151.9, 134.9, 133.1, 130.1, 129.7, 129.4, 129.2, 128.8, 128.5, 127.3, 122.4, 121.3, 118.1, 96.8, 68.9, 62.7, 62.1, 47.4, 14.1, 13.5; ESI-HRMS: calcd. for $C_{29}H_{27}ClN_2O_7$+H 551.16003, found 551.15796; $[\alpha]_D^{25} = -11.3$ (*c* 0.80, CH_2Cl_2), 17% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), $t_{minor} = 9.17$ min, $t_{major} = 19.75$ min.

3-Phenyl-4-(4-bromophenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5c). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, $J = 7.6$ Hz, 1H), 7.35-7.06 (m, 10H), 6.97

(t, J = 7.6 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.65 (s, 1H), 5.60 (s, 1H), 5.51 (d, J = 5.2 Hz, 1H), 4.48-4.41 (m, 2H), 3.59-3.37 (m, 2H), 3.18 (d, J = 5.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6, 168.7, 151.7, 135.9, 133.6, 131.4, 130.1, 130.0, 129.4, 129.3, 127.3, 123.2, 121.3, 118.1, 76.7, 69.0, 62.7, 62.1, 47.4, 45.8, 14.1, 13.4; ESI-HRMS: calcd. for $C_{29}H_{27}BrN_2O_7$+Na 617.09180, found 617.08938; $[\alpha]_D^{25} = -18.3$ (c 0.76, CH_2Cl_2), 35% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 10.45 min, t_{major} = 21.37 min.

3-Phenyl-4-(4-(trifluoromethyl)phenyl)-3a-nitrobenzopyrano-[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5d). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58-7.29 (m, 10H), 7.14-6.99 (m, 2H), 6.78 (d, J = 8.0 Hz, 1H), 5.73-5.71 (m, 2H), 5.56 (d, J = 4.8 Hz, 1H), 4.51-4.46 (m, 2H), 3.84-3.64 (m, 2H), 3.24 (d, J = 4.8 Hz, 1H), 1.42 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6, 168.7, 151.8, 138.5, 131.0, 130.8, 129.5, 129.3, 128.9, 128.8, 127.3, 125.3,125.2, 125.1, 125.0, 122.6, 122.4, 121.1, 118.1, 96.7, 68.9, 62.8, 62.2, 47.3, 14.1, 13.5; ESI-HRMS: calcd. for $C_{30}H_{27}F_3N_2O_7$+Na 607.16791, found 607.16626; $[\alpha]_D^{25} = -22.6$ (c 0.69, ethanol), 49% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 7.16 min, t_{major} = 13.53 min.

3-Phenyl-4-(4-methylphenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5e). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (d, J = 7.6 Hz, 1H), 7.35-6.91 (m, 11H), 6.72 (d, J = 8.0 Hz, 1H), 5.67 (s, 1H), 5.64 (s, 1H), 5.53 (d, J = 1.6 Hz, 1H), 4.47-4.42 (m, 2H), 3.72-3.59 (m, 2H), 3.17 (d, J = 3.6 Hz, 1H), 2.21 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7, 169.8, 152.0, 138.7, 136.0, 131.4, 130.0, 129.3, 129.0, 128.8, 128.2, 127.3, 121.7, 118.2, 96.9, 68.1, 62.7, 62.1, 47.6, 21.1, 14.1, 13.5. IR (KBr) cm^{-1} 3345, 1741, 1712, 1582, 1489, 1458, 768; ESI-HRMS: calcd. for $C_{30}H_{30}N_2O_7$+H 531.21415, found 531.21407; $[\alpha]_D^{25} = -28.6$ (c 0.48, ethanol), 45% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 8.96 min, t_{major} = 11.52 min.

3-Phenyl-4-(4-methoxyphenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5f). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 7.6 Hz, 1H), 7.36-7.09 (m, 10H), 6.97 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.64 (d, J = 10.2 Hz, 2H), 5.51 (d, J = 7.6 Hz, 1H), 4.50-4.40 (m, 2H), 3.78-3.60 (m, 2H), 3.19-3.17 (m, 3H), 1.42-1.37 (m, 3H), 0.94 (t, J = 10.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6, 168.7, 151.9, 134.9, 133.1, 130.1, 129.7, 129.4, 129.2, 128.8, 128.4, 127.3, 122.4, 121.3, 118.1, 96.8, 68.9, 62.7, 62.1, 47.4, 14.0, 13.8; ESI-HRMS: calcd. for $C_{30}H_{30}N_2O_8$+Na 541.97903, found 541.97815; $[\alpha]_D^{25} = -28.6$ (c 0.50, ethanol), 21% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 11.13 min, t_{major} = 14.13 min.

Diethyl 8-fluoro-3-phenyl-4-phenyl-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5g). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35-7.18 (m, 12H), 6.80-6.68 (m, 2H), 5.65-5.51 (m, 3H), 4.51-4.40 (m, 2H), 3.87-3.71 (m, 2H), 3.19 (d, J = 4.8 Hz, 1H), 1.39 (t, J = 5.2 Hz, 3H), 0.92 (t, J = 3.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.5, 169.6, 135..0, 134.2, 129.3, 128.8, 128.3, 128.3, 127.3, 119.3, 119.2, 116.4, 116.2, 116.1, 115.8, 96.5, 68.8, 62.8, 62.3, 47.6, 14.0, 13.4; ESI-HRMS: calcd. for $C_{29}H_{27}FN_2O_7$+Na 557.17051, found 557.16945; $[\alpha]_D^{25} = -23.3$ (c 0.56, ethanol), 53% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 10.78 min, t_{major} = 23.81 min.

Diethyl 9-methoxy-3-phenyl-4-phenyl-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5h). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.22 (m, 12H), 6.55-6.52 (m, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.62 (d, J = 2.8 Hz, 1H), 5.50 (d, J = 4.2 Hz, 1H), 4.47-4.42 (m, 2H), 3.84-3.65 (m, 5H), 3.16 (d, J = 4.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 168.9, 160.2, 153.0, 134.5, 130.7, 129.3, 128.8, 128.3, 127.3, 96.9, 62.8, 62.5, 62.1, 56.3, 47.2, 14.1, 13.6; $C_{30}H_{30}N_2O_8$+Na 541.97917, found 541.97873; $[\alpha]_D^{25} = -13.1$ (c 0.70, ethanol), 33% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (30% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 11.1 min, t_{major} = 18.41 min.

Diethyl 9-methoxy-3-phenyl-4-(4-methylphenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5i). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40-7.26 (m, 6H), 7.09-7.00 (m, 4H), 6.55-6.52 (m, 1H), 6.30 (d, J = 1.2 Hz, 1H), 5.60 (d, J = 7.2 Hz, 2H), 6.51 (s, 1H), 4.47-4.42 (m, 2H), 3.81-3.66 (m, 5H), 3.16 (d, J = 5.2 Hz, 1H), 2.25 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8, 169.9, 160.2, 153.3, 138.7, 136.2, 131.4, 130.6, 129.2, 128.9, 128.7, 127.3, 113.4, 109.1, 102.1, 96.9, 68.9, 62.6, 62.1, 55.3, 47.2, 21.1, 14.1, 13.6; ESI-HRMS: calcd. for $C_{31}H_{32}N_2O_8$+H 561.22455, found 561.22391; $[\alpha]_D^{25} = -19.6$ (c 0.65, ethanol), 57% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), t_{major} = 5.69 min, t_{minor} = 7.04 min.

Diethyl 9-methoxy-3-phenyl-4-(4-methoxyphenyl)-3a-nitrobenzopyrano[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5j). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.11 (m, 8H), 6.74-6.52 (m, 3H), 6.30 (d, J = 2.4 Hz, 1H), 5.61 (s, 1H), 5.58 (s, 1H), 5.49 (s, 1H), 4.46-4.42 (m, 2H), 3.84-3.62 (m, 8H), 3.15 (s, 1H), 1.39 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.2, 159.8, 130.5, 129.7, 129.2, 128.7, 127.3, 126.6, 113.7, 110.1, 109.1, 102.7, 97.0, 68.9, 62.5, 55.2, 55.1, 47.1, 14.1, 13.6; ESI-HRMS: calcd. for $C_{31}H_{32}N_2O_9$+Na 599.20127, found 599.20095; $[\alpha]_D^{25} = -21.1$ (c 0.540, ethanol), 70% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), t_{minor} = 5.71 min, t_{major} = 7.08 min.

9-Methoxy-3-phenyl-4-(4-chlorophenyl)-3a-nitrobenzopyrano-[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5k). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.14 (m, 10H), 6.56-6.33 (m, 1H), 6.28 (d, J = 2.4 Hz, 1H), 5.59 (d, J = 6.0 Hz, 2H), 5.47 (d, J = 4.0 Hz, 1H), 4.47-4.39 (m, 2H), 3.85-3.65 (m, 5H), 3.15 (d, J = 4.0 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.9, 160.3, 134.9, 133.1, 130.7, 129.7, 129.3, 128.8, 128.5, 127.3, 109.4, 102.6, 96.7, 68.8, 62.6, 62.1, 55.2, 47.0, 14.0, 13.5; ESI-HRMS: calcd. for $C_{30}H_{29}ClN_2O_8$+H 581.16998, found 581.16879; $[\alpha]_D^{25} = -15.8$ (c 0.40, ethanol), 51% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD

column (10% 2-propanol–hexane, 0.5 mL min^{-1}), $t_{major} = 6.26$ min, $t_{minor} = 7.00$ min.

9-Methoxy-3-phenyl-4-(4-bromophenyl)-3a-nitrobenzopyrano-[3,4-*c*]-pyrrolidine-1,1-dicarboxylate (5l). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.26 (m, 8H), 7.10-7.08 (m, 2H), 6.56-6.54 (m, 1H), 6.29 (d, $J = 6.4$ Hz, 1H), 5.59 (s, 2H), 5.48 (s, 1H), 4.48-4.41 (m, 2H), 3.85-3.66 (m, 5H), 3.16 (s, 1H), 1.39 (t, $J = 7.2$ Hz, 3H), 1.00 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7, 168.8, 160.3, 152.9, 136.0, 133.6, 131.5, 130.7, 130.0, 129.4, 128.8, 127.3, 123.2, 113.0, 109.4, 102.7, 96.7, 68.8, 62.6, 62.1, 55.3, 47.0, 14.1, 13.6; ESI-HRMS: calcd. for $C_{30}H_{29}BrN_2O_8$+H 625.11800, found 625.11820; $[\alpha]_D^{25} = -17.2$ (*c* 0.34, ethanol), 13% ee; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 0.5 mL min^{-1}), $t_{major} = 13.78$ min, $t_{minor} = 24.97$ min.

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