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Enantioselective Synthesis of Chromans with a Quaternary Stereogenic Centre through Catalytic Asymmetric Cascade Reactions

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1. General methods

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed using 200-300 mesh silica gel. ^1H NMR spectra were recorded on Varian Mercury 400/600 (400/600 MHz) spectrophotometers. Chemical shifts (δ) are reported in ppm from the solvent resonance as the internal standard (CDCl_3 : 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Mercury 400/600 (100/150 MHz) with complete proton decoupling spectrophotometers (CDCl_3 : 77.0 ppm). Mass spectra were measured on API 2000 LC/MS/MS (ESI-MS) or Waters Synapt G2 (MALDI). Enantiomeric ratios were determined by chiral HPLC on Agilent 1100 series with chiral columns (chiralpak AS-H column, chiralpak AD-H column) with hexane and 2-propanol as solvents. Optical rotations were measured with JASCO P-1020 polarimeter.

2. Materials

All substrates were prepared according to literature procedures¹ and characterizations of nitroolefin enoates were in accordance with previously reported data.

Reference

1 (a) Ciganek, E. *Synthesis* **1995**, 1311-1314. (b) Denmark, S. E.; Senanayaket, C. B. W. *J. Org. Chem.* **1993**, 58, 1853-1858. (c) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.*, **2008**, 130, 13862-13863; (d) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem. Int. Ed.*, **2009**, 48, 9542-9545. (e) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.*, **2010**, 49, 8379-8383.

3. Reaction Optimisation

Table 1s. The screening of solvent for the cascade aza-Michael/Michael addition reaction.^[a]

Entry	Solvents	t (d)	Product	Yield[%] ^[b]	ee (%) ^[c]	dr ^[c]
1	CH₂Cl₂	5	3a	90	87	81:19
2	CHCl ₃	5	3a	52	73	75:25
3	ClCH ₂ CH ₂ Cl	6	3a	81	85	80:20
4	THF	6	3a	32	71	78:22
5	Et ₂ O	6	3a	70	77	84:16
6	CH ₃ CN	5	3a	96	73	85:15
7	Toluene	5	3a	78	67	76:24
8	xylenes	5	3a	70	65	75:25
9	CH ₃ OH	7	3a	75	13	83:17
10	CH ₃ CH ₂ OH	7	3a	82	32	73:27
11	Hexane	7	3a	72	73	77:23
12	^t BuOMe	7	3a	87	81	83:17
13	DMF	7	3a	72	6	93:7

[a] Reactions were carried out with **1a** (0.40mmol), **2a** (0.60mmol), Catalyst **I** (0.04mmol) in solvent (2.0 ml) at 10 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC.

Table 2s. The screening of temperature for the cascade aza-Michael/Michael addition reaction.^[a]

Entry	Temperature(°C)	t (d)	Product	Yield[%] ^[b]	ee (%) ^[c]	dr ^[c]
1	0	12	3a	71	86	82:18
2	10	5	3a	90	87	81:19
3	25	5	3a	57	80	80:20

[a] Reactions were carried out with **1a** (0.40mmol), **2a** (0.60mmol), Catalyst **I** (0.04mmol) in CH₂Cl₂ (2.0 ml) at x °C. [b] Yield of isolated product. [c] Determined by chiral HPLC.

Table 3s. The screening of bifunctional catalyst for the cascade aza-Michael/Michael addition reaction.^[a]

[a] Reactions were carried out with **1a** (0.40mmol), **2a** (0.60mmol), Catalyst (0.04mmol) in CH₂Cl₂ (2.0 ml) at 10 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC.

Table 4s. The screening of equivalent of benzotriazole **2a** for the cascade aza-Michael/Michael addition reaction.^[a]

Entry	Equivalent of 2a	t (d)	Product	Yield[%] ^[b]	ee (%) ^[c]	dr ^[c]
1	1.5	5	3a	77	92	91:9
2	2.0	5	3a	78	87	86:14
3	3.0	5	3a	83	81	83:17

[a] Reactions were carried out with **1a** (0.40mmol), **2a**, Catalyst **III** (0.04mmol) in CH_2Cl_2 (2.0 ml) at 10°C . [b] Yield of isolated product. [c] Determined by chiral HPLC.

4. General Procedure and Spectral Data of Products

General procedure for the asymmetric cascade aza-Michael/Michael addition reaction.

A mixture of nitroolefin enoate **1a** (0.40 mmol) and catalyst **III** (0.040 mmol) in CH_2Cl_2 (2.0 mL) was stirred at 10°C for 15 min, then benzotriazole **2a** (0.60 mmol) was added to the reaction mixture. Upon completion (monitored by TLC analysis), the mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 7/1 to 5/1 as eluants) to afford the desired product **3a**.

Ethyl 2-((2*R*,3*S*,4*R*)-4-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3a**).** Prepared according to the general procedure from **1a** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10°C for 5 d to provide the title compound as a white solid (77% yield, 92% ee, 91:9 dr). ¹H NMR (600 MHz, CDCl_3) δ (ppm) 8.12 (d, $J = 8.5$ Hz, 1H), 7.43 – 7.39 (m, 2H), 7.35 – 7.32 (m, 2H), 7.07 – 7.06 (m, 1H), 6.95 – 6.92 (m, 1H), 6.56 (s, 1H), 5.31 (d, $J = 9.7$ Hz, 1H), 4.28 – 4.24 (m, 2H), 2.84 (dd, $J = 16.0, 9.8$ Hz, 1H), 2.42 (d, $J = 16.4$ Hz, 1H), 1.54 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H); ¹³C NMR (150 MHz, CDCl_3) δ (ppm) 168.58, 152.83, 145.55,

130.33, 127.98, 124.30, 122.52, 120.25, 117.31, 88.75, 76.29, 63.05, 61.26, 34.56, 13.97, 12.23; **HRMS** (ESI): Calcd for C₂₀H₂₀N₄O₅ [M+Na]: 419.1331. Found: 419.1315; [α]_D²⁹ = 43.20 (c = 1.04, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, t_{major} = 43.03 min, t_{minor} = 24.53 min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-fluoro-3-methyl-3-nitrochroman-2-yl)acetate (3b). Prepared according to the general procedure from **1b** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 7 days to provide the title compound as a white solid (73% yield, 90% ee, 85:15 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.13 (d, *J* = 8.3 Hz, 1H), 7.48 – 7.47 (m, 1H), 7.44 – 7.41 (m, 1H), 7.28 – 7.27 (m, 1H), 7.06 – 7.03 (m, 2H), 6.24 (s, 1H), 5.29 (d, *J* = 9.7 Hz, 1H), 4.27 – 4.23 (m, 2H), 2.84 (dd, *J* = 16.3, 9.9 Hz, 1H), 2.42 (d, *J* = 16.3 Hz, 1H), 1.55 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ (ppm) 168.62, 158.61, 157.00, 149.08, 145.60, 128.51, 124.65, 120.56, 118.90, 117.87, 117.71, 114.32, 114.15, 88.65, 76.73, 61.46, 34.63, 14.08, 12.39; **HRMS** (ESI): Calcd for C₂₀H₁₉FN₄O₅ [M+Na]: 437.1237. Found: 437.1231; [α]_D²⁹ = 26.66 (c = 1.11, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, t_{major} = 16.61 min, t_{minor} = 14.70 min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-chloro-3-methyl-3-nitrochroman-2-yl)acetate (3c). Prepared according to the general procedure from **1c** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (77% yield, 89% ee, 90:10 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.14 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.45 – 7.42 (m, 1H), 7.29 – 7.25 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.51 (s, 1H), 5.30 (d, *J* = 9.7 Hz, 1H), 4.27 – 4.23 (m, 2H), 2.85 (dd, *J* = 16.3, 9.9 Hz, 1H), 2.42 (d, *J* = 16.3 Hz, 1H), 1.56 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ (ppm) 168.51, 151.47, 145.49, 130.56, 128.50, 127.81, 127.56, 124.65, 120.49, 118.85, 88.46, 76.64, 61.43, 34.54, 14.06, 12.33; **HRMS** (ESI): Calcd for C₂₀H₁₉ClN₄O₅ [M+Na]: 453.0942. Found: 453.0933; [α]_D²⁸ = 52.25 (c = 1.04, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, t_{major} = 21.81 min, t_{minor} = 16.32 min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-bromo-3-methyl-3-nitrochroman-2-yl)acetate (3d). Prepared according to the general procedure from **1d** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (76% yield, 89% ee, 89:11 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.13 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.48 (m, 1H), 7.44 – 7.41 (m, 2H), 7.28 – 7.27 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.65 (s, 1H), 5.30 (d, *J* = 9.8 Hz, 1H), 4.26 – 4.23 (m, 2H), 2.85 (dd, *J* = 16.3, 9.9 Hz, 1H), 2.42 (d, *J* = 16.4, 1H), 1.55 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz,

CDCl₃) δ (ppm) 168.50, 151.98, 145.48, 133.44, 130.46, 128.51, 124.66, 120.49, 119.20, 114.97, 109.63, 88.41, 76.59, 62.14, 61.44, 34.53, 14.03, 12.33; **HRMS** (ESI): Calcd for C₂₀H₁₉BrN₄O₅ [M+Na]: 497.0437. Found: 497.0419; $[\alpha]_D^{29} = 51.08$ (c = 1.06, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 25.66$ min, $t_{\text{minor}} = 17.64$ min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3,6-dimethyl-3-nitrochroman-2-yl)acetate (3e). Prepared according to the general procedure from **1e** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (88% yield, 90% ee, 86:14 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.12 (d, $J = 8.1$ Hz, 1H), 7.51 – 7.36 (m, 2H), 7.29 (s, 1H), 7.12 (d, $J = 8.1$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 6.34 (s, 1H), 5.27 (d, $J = 9.5$ Hz, 1H), 4.26 – 4.23 (m, 2H), 2.83 (dd, $J = 16.0, 10.0$ Hz, 1H), 2.41 (d, $J = 16.1$ Hz, 1H), 2.11 (s, 3H), 1.52 (s, 3H), 1.31 (t, $J = 7.0$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 168.69, 150.82, 145.58, 133.61, 132.20, 131.20, 128.09, 127.90, 124.38, 120.34, 117.17, 116.72, 110.10, 89.01, 76.38, 63.04, 61.30, 34.67, 20.40, 14.03, 12.29; **HRMS** (ESI): Calcd for C₂₁H₂₂N₄O₅ [M+Na]: 433.1488. Found: 433.1475; $[\alpha]_D^{29} = 55.38$ (c = 1.22, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 18.99$ min, $t_{\text{minor}} = 13.43$ min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-6-methoxy-3-methyl-3-nitrochroman-2-yl)acetate (3f). Prepared according to the general procedure from **1f** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (82% yield, 90% ee, 95:5 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.12 (d, $J = 8.3$ Hz, 1H), 7.43 – 7.39 (m, 2H), 7.31 – 7.28 (m, 1H), 7.00 – 6.99 (m, 1H), 6.90 – 6.89 (m, 1H), 6.03 (s, 1H), 5.25 (d, $J = 9.7$ Hz, 1H), 4.27 – 4.23 (m, 2H), 3.51 (s, 3H), 2.82 (dd, $J = 16.1, 9.9$ Hz, 1H), 2.39 (d, $J = 16.1$ Hz, 1H), 1.50 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ (ppm) 13C NMR (101 MHz, cdcl3) δ 168.75, 154.85, 146.96, 145.64, 133.39, 128.20, 124.45, 120.43, 118.42, 117.05, 111.88, 110.20, 89.14, 76.48, 63.26, 61.37, 55.59, 34.66, 14.07, 12.34; **HRMS** (ESI): Calcd for C₂₁H₂₂N₄O₆ [M+Na]: 449.1437. Found: 449.1425; $[\alpha]_D^{28} = 39.81$ (c = 1.01, CHCl₃); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 22.92$ min, $t_{\text{minor}} = 19.28$ min).

Ethyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-7-methoxy-3-methyl-3-nitrochroman-2-yl)acetate (3g). Prepared according to the general procedure from **1g** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH₂Cl₂ (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (82% yield, 91% ee, 90:10 dr). **¹H NMR** (600 MHz, CDCl₃) δ (ppm) 8.10 (d, $J = 8.1$ Hz, 1H), 7.46 – 7.35 (m, 2H), 7.28 (s, 1H), 7.02 (s, 1H), 6.58

(s, 1H), 6.58 (s, 1H), 6.52 – 6.48 (m, 2H), 5.30 (d, $J = 8.9$ Hz, 1H), 4.27 – 4.24 (m, 2H), 3.80 (s, 3H), 2.82 (dd, $J = 16.2, 10.0$ Hz, 1H), 2.41 (d, $J = 15.2$ Hz, 1H), 1.48 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.72, 161.18, 154.06, 145.73, 133.28, 128.95, 128.04, 124.34, 120.39, 110.15, 101.69, 89.05, 76.45, 61.40, 55.44, 34.64, 14.07, 12.33, 12.24; HRMS (ESI): Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_6$ $[\text{M}+\text{Na}]$: 449.1437. Found: 449.1417; $[\alpha]_{\text{D}}^{29} = 44.07$ ($c = 1.02$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 19.20$ min, $t_{\text{minor}} = 17.57$ min).

Methyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3h). Prepared according to the general procedure from **1b** (0.40 mmol), **2h** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (84% yield, 92% ee, 92:8 dr). ^1H NMR (600 MHz, CDCl_3) δ (ppm) 8.12 – 8.10 (m, 1H), 7.44 – 7.36 (m, 2H), 7.33 – 7.28 (m, 2H), 7.07 – 7.06 (m, 1H), 6.93 – 6.91 (m, 1H), 6.55 (s, 1H), 5.32 (d, $J = 9.8$ Hz, 1H), 3.79 (s, 3H), 2.86 (dd, $J = 16.1, 10.0$ Hz, 1H), 2.43 (d, $J = 16.3$ Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 169.06, 152.78, 145.55, 130.33, 127.97, 124.29, 122.53, 120.25, 117.33, 110.13, 88.73, 76.20, 63.09, 52.23, 34.31, 12.24; HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_5$ $[\text{M}+\text{Na}]$: 405.1175. Found: 405.1164. $[\alpha]_{\text{D}}^{29} = 41.53$ ($c = 1.07$ CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 39.99$ min, $t_{\text{minor}} = 28.73$ min).

Tert-butyl 2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3i). Prepared according to the general procedure from **1i** (0.40 mmol), **2a** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 7 days to provide the title compound as a white solid (91% yield, 90% ee, 86:14 dr). ^1H NMR (600 MHz, CDCl_3) δ (ppm) 8.11 (d, $J = 8.2$ Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 – 7.32 (m, 2H), 7.05 (d, $J = 8.2$ Hz, 1H), 6.92 (t, $J = 7.6$ Hz, 1H), 6.55 (s, 1H), 5.23 (d, $J = 8.9$ Hz, 1H), 2.74 (dd, $J = 15.9, 9.9$ Hz, 1H), 2.37 (d, $J = 15.2$ Hz, 1H), 1.51 (s, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 167.73, 153.01, 145.63, 130.39, 128.07, 124.35, 122.57, 120.35, 117.35, 88.84, 81.93, 76.72, 63.06, 35.75, 27.94, 12.34; HRMS (ESI): Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_5$ $[\text{M}+\text{Na}]$: 447.1644. Found: 447.1639; $[\alpha]_{\text{D}}^{29} = 35.68$ ($c = 1.00$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AD column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 11.09$ min, $t_{\text{minor}} = 12.10$ min).

Ethyl 2-((2R,3S,4R)-4-(5,6-dimethyl-1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3j). Prepared according to the general procedure from **1a** (0.40 mmol), **2b** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (90% yield, 96% ee, 96:4 dr). ^1H NMR (600 MHz, CDCl_3) δ (ppm) 7.81 (s, 1H), 7.32 – 7.25 (m, 2H), 7.04 (d, $J = 8.1$ Hz, 1H), 6.90 (t, $J = 7.5$ Hz, 1H), 6.52 (s, 1H), 5.30 (d, $J = 9.8$ Hz, 1H), 4.26 – 4.23 (m, 2H), 2.84 (dd, $J = 16.1, 9.9$ Hz, 1H), 2.42 (d, $J = 16.1$ Hz,

1H), 2.38 (s, 3H), 2.32 (s, 3H), 1.55 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.67, 152.80, 144.83, 138.45, 134.23, 132.76, 130.24, 128.03, 122.51, 119.28, 117.26, 109.48, 88.80, 76.39, 62.92, 61.29, 34.66, 20.92, 20.17, 14.01, 12.29; HRMS (MALDI); Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 425.1825; Found: 425.1833; $[\alpha]_{\text{D}}^{27} = 24.95$ ($c = 1.03$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 38.47$ min, $t_{\text{minor}} = 21.99$ min).

Ethyl 2-((2R,3S,4R)-4-(5,6-dimethyl-1H-benzo[d][1,2,3]triazol-1-yl)-6-fluoro-methyl-3-nitrochroman-2-yl)acetate (3k). Prepared according to the general procedure from **1b** (0.40 mmol), **2b** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 7 days to provide the title compound as a white solid (82% yield, 91% ee, 90:10 dr). ^1H NMR (600 MHz, CDCl_3)

δ (ppm) 7.85 (s, 1H), 7.18 (s, 1H), 7.02 (s, 2H), 6.20 (s, 1H), 5.27 (d, $J = 9.6$ Hz, 1H), 4.27 – 4.24 (m, 2H), 2.84 (dd, $J = 15.9, 10.0$ Hz, 1H), 2.44 (d, $J = 14.1$ Hz, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 1.57 (s, 3H), 1.32 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.68, 158.54, 156.93, 148.93, 144.66, 139.05, 134.58, 119.41, 118.71, 117.67, 117.51, 114.26, 114.09, 88.59, 76.70, 61.42, 34.60, 21.02, 20.27, 14.04, 12.38; HRMS (MALDI); Calcd for $\text{C}_{22}\text{H}_{23}\text{FN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 443.1731; Found: 443.1743; $[\alpha]_{\text{D}}^{28} = 14.27$ ($c = 1.03$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 35.55$ min, $t_{\text{minor}} = 16.49$ min).

Ethyl 2-((2R,3S,4R)-6-chloro-4-(5,6-dimethyl-1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3l). Prepared according to the general procedure from **1c** (0.40 mmol), **2b** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (80% yield, 90% ee, 90:10 dr). ^1H NMR (600

MHz, CDCl_3) δ (ppm) 7.85 (s, 1H), 7.27 (s, 2H), 7.15 (s, 1H), 6.99 (d, $J = 8.6$ Hz, 1H), 6.45 (s, 1H), 5.28 (d, $J = 9.7$ Hz, 1H), 4.27 – 4.24 (m, 2H), 2.84 (dd, $J = 16.1, 9.9$ Hz, 1H), 2.44 (d, $J = 13.8$ Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.59 (s, 3H), 1.31 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.61, 151.35, 144.66, 139.13, 134.63, 130.43, 127.77, 127.53, 119.42, 118.76, 88.44, 76.68, 61.44, 34.58, 21.05, 20.31, 14.05, 12.39; HRMS (MALDI); Calcd for $\text{C}_{22}\text{H}_{23}\text{ClN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 459.1435 Found: 459.1445; $[\alpha]_{\text{D}}^{29} = 39.77$ ($c = 1.24$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 30.56$ min, $t_{\text{minor}} = 16.44$ min).

Ethyl 2-((2R,3S,4R)-6-bromo-4-(5,6-dimethyl-1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)acetate (3m). Prepared according to the general procedure from **1d** (0.40 mmol), **2b** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (70% yield, 91% ee, 90:10 dr). ^1H NMR (600

MHz, CDCl_3) δ (ppm) 7.85 (s, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 7.15 (s, 1H), 6.93 (d, $J = 8.6$ Hz, 1H),

6.60 (s, 1H), 5.28 (d, $J = 9.7$ Hz, 1H), 4.27 – 4.23 (m, 2H), 2.84 (dd, $J = 16.1, 9.9$ Hz, 1H), 2.43 (s, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.59 (s, 3H), 1.31 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.56, 151.83, 144.57, 139.08, 137.55, 134.59, 133.26, 132.90, 130.40, 125.18, 119.38, 119.08, 114.90, 88.36, 76.61, 61.41, 34.54, 21.03, 20.28, 20.22, 14.04, 12.35; **HRMS** (MALDI); Calcd for $\text{C}_{22}\text{H}_{23}\text{BrN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 503.0930; Found: 503.0945; $[\alpha]_{\text{D}}^{29} = 38.58$ ($c = 1.39$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 32.29$ min, $t_{\text{minor}} = 17.94$ min).

Ethyl 2-((2R,3S,4R)-4-(5,6-dimethyl-1H-benzo[d][1,2,3]triazol-1-yl)-7-methoxy-3-methyl-3-nitrochroman-2-yl)acetate (3n). Prepared according to the general procedure from **1g** (0.40 mmol), **2b** (0.60 mmol), catalyst **III** (0.040 mmol) and CH_2Cl_2 (2.0 mL) at 10 °C for 5 days to provide the title compound as a white solid (85% yield, 93% ee, 91:9 dr).

^1H NMR (600 MHz, CDCl_3) δ (ppm) 7.82 (s, 1H), 7.27 – 7.18 (m, 2H), 6.56 (s, 1H), 6.51 – 6.50 (m, 1H), 6.44 (s, 1H), 5.29 (d, $J = 9.8$ Hz, 1H), 4.26 – 4.25 (m, 2H), 3.80 (s, 3H), 2.84 – 2.80 (m, 1H), 2.42 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 1.51 (s, 3H), 1.32 (t, $J = 5.4$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) 168.70, 160.99, 153.84, 144.82, 138.45, 134.17, 128.82, 119.22, 109.95, 101.52, 88.95, 76.40, 61.29, 55.34, 34.58, 20.88, 20.21, 20.14, 14.03, 12.21; **HRMS** (MALDI); Calcd for $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_6$ $[\text{M}+\text{Na}]^+$: 477.1750; Found: 477.1766; $[\alpha]_{\text{D}}^{28} = 34.65$ ($c = 1.09$, CHCl_3); the enantiomeric excess was determined by chiral HPLC (Chiralpak AS column: hexane/2-propanol = 60/40, 0.5 mL/min, 254 nm, $t_{\text{major}} = 53.93$ min, $t_{\text{minor}} = 26.65$ min).

Ethyl 2-((2R,3S,4R)-4-((2-hydroxyphenyl)amino)-3-methyl-3-nitro-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (3o)

Prepared according to the general procedure from **1a** (0.40 mmol), **2-aminophenol** (0.60 mmol), CH_2Cl_2 (2.0 mL) at rt for 48 h to provide the title compound as a pale yellow oil (67% yield, 86% ee, 97:3 d.r.). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.17-7.25 (m, 1H), 6.93 (t, $J = 7.2$ Hz, 1H),

6.75-6.84 (m, 3H), 6.61-6.73 (m, 2H), 5.76-5.78 (m, 2H), 5.17 (dd, $J = 9.6, 2.4$ Hz, 1H), 4.21-4.26 (m, 2H), 2.75 (dd, $J = 16.0, 10.0$ Hz, 2H), 2.39 (d, $J = 16.0$ Hz, 1H), 1.57 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 169.53, 152.30, 142.81, 135.74, 129.42, 127.39, 123.57, 122.35, 121.87, 118.70, 116.48, 114.74, 112.02, 88.57, 76.43, 61.44, 59.43, 35.10, 14.10, 10.49. **HRMS** (ESI): Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{S}$ $[\text{M}+\text{Na}]^+$: 409.1376. Found: 409.1352. $[\alpha]_{\text{D}}^{29} = -8.28$ ($C = 1.00$, CHCl_3). HPLC (Chiralpak AD-H column, hexane/2-propanol = 85:15, 1.0 mL/min; 254 nm, 25 °C, $t_1 = 8.06$ min, $t_2 = 9.69$ min, $t_3 = 11.71$ min, $t_4 = 15.56$ min).

5. Synthesis transformation of the cascade reaction adduct 3a

Ethyl 2-((2R,3S,4R)-3-amino-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methylchroman-2-yl)acetate (4a). To a two-necked 10-mL flask were sequentially added (1.89 g, 10 mmol) of anhydrous tin(II) chloride in Glove Box and a solution of **3a** (0.40 g, 1.0 mmol) in 12.5 mL of EtOH containing (10 mmol HCl, prepared from 10 mmol of acetic chloride at 0 °C) under nitrogen atmosphere. The reaction mixture was heated to reflux for 4 h. It was then cooled to 0 °C, quenched with sat. NH_4Cl and basified with $\text{NH}_3\cdot\text{H}_2\text{O}$. Dichloromethane was added and vigorously stirred for 10 min. The white suspension was suction filtrated over Celit. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4 . Then the crude product was purified by flash silica gel chromatography to afford the product **4a** as white solid in 89 % yield. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm) 8.09 (d, $J = 8.3$ Hz, 1H), 7.34 – 7.30 (m, 1H), 7.27 – 7.24 (m, 2H), 7.00 (d, $J = 8.1$ Hz, 1H), 6.81 (t, $J = 7.4$ Hz, 1H), 6.56 (s, 1H), 6.31 (s, 1H), 4.73 (d, $J = 6.3$ Hz, 1H), 4.26 – 4.24 (m, 2H), 3.14 (d, $J = 15.9$ Hz, 1H), 2.73 (dd, $J = 15.9, 9.0$ Hz, 1H), 1.57 (s, 2H), 1.31 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm) 171.21, 154.35, 146.15, 129.72, 128.23, 126.93, 123.72, 121.32, 120.01, 117.22, 79.62, 60.77, 60.22, 53.09, 34.70, 16.94, 14.14; **HRMS** (MALDI); Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_3$ [$\text{M}+\text{Na}$]: 389.1590; Found: 389.1591.

2-((2R,3S,4R)-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methyl-3-nitrochroman-2-yl)ethanol (5a). To a solution of the nitro **3a** (0.40 g, 1.0 mmol) in dichloromethane (0.06 M) at -78°C , was added DIBAL-H (4.0 eq, 1M solution in hexane), the reaction was left to warm to room temperature overnight. The reaction was quenched with aqueous hydrochloric acid (1.0 M) and water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the alcohol **5a**, which was purified by column chromatograph (petroleum ether / ethyl acetate = 5/1) as a white solid in 88% yield. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm) 8.10 (d, $J = 7.1$ Hz, 1H), 7.38 (s, 2H), 7.35 – 7.26 (m, 2H), 7.07 – 7.06 (m, 1H), 6.91 (t, $J = 7.1$ Hz, 1H), 6.56 (s, 1H), 4.99 (d, $J = 9.5$ Hz, 1H), 3.96 (s, 2H), 2.56 (s, 1H), 2.06 – 2.02 (m, 1H), 1.65 – 1.61 (m, 1H), 1.50 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm) 153.17, 145.62, 130.38, 128.18, 128.09, 124.44, 122.45, 120.30, 117.38, 89.53, 77.03, 58.26, 31.61, 12.05; **HRMS** (MALDI); Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_4$ [$\text{M}+\text{Na}$]: 377.1226; Found: 377.1226.

2-((2R,3S,4R)-3-amino-4-(1H-benzo[d][1,2,3]triazol-1-yl)-3-methylchroman-2-yl)ethanol (6a).

To a two-necked 10-mL flask were sequentially added (0.81 g, 4.3 mmol) of anhydrous tin(II) chloride in Glove Box and a solution of 3a (0.15 g, 0.43 mmol) in 5.4 mL of EtOH containing (4.3 mmol HCl, prepared from 4.3 mmol of acetic chloride at 0 °C) under nitrogen atmosphere. The reaction mixture was heated to reflux for 4 h. It was then cooled to 0 °C, quenched with sat. NH_4Cl and basified with $\text{NH}_3 \cdot \text{H}_2\text{O}$. Dichloromethane was added and vigorously stirred for 10 min. The white suspension was suction filtrated over Celit. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4 . Then the crude product was purified by flash silica gel chromatography to afford the product **6a** as white solid in 88 % yield. **^1H NMR** (600 MHz, CDCl_3) δ (ppm) 8.08 (d, $J = 8.3$ Hz, 1H), 7.42 – 7.17 (m, 3H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.78 (t, $J = 7.4$ Hz, 1H), 6.54 (s, 1H), 6.31 (s, 1H), 4.34 (s, 1H), 4.02 – 3.84 (m, 2H), 2.65 (s, 3H), 2.28 – 2.24 (m, 1H), 2.03 – 1.99 (m, 1H), 0.91 (s, 3H); **^{13}C NMR** (150 MHz, CDCl_3) δ (ppm) 154.41, 146.07, 129.75, 128.27, 128.24, 127.02, 123.84, 121.21, 119.96, 117.11, 81.21, 65.69, 59.12, 53.18, 32.20, 17.23; **HRMS** (MALDI); Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2$ [$\text{M}+\text{Na}$]: 347.1484; Found: 347.1473.

6. Copies of ^1H NMR and ^{13}C NMR Spectrums

7. The copy of HPLC chromatograms

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.726	VV	0.3177	3150.48584	151.87851	50.3087
2	17.002	VV	0.4556	3111.82690	103.50383	49.6913

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.707	VV	0.3190	731.01971	35.06178	5.2465
2	16.618	VV	0.5409	1.32025e4	357.99628	94.7535

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.331	VV	0.3727	5194.63574	212.42064	50.1137
2	22.715	BB	1.0409	5171.06494	73.60546	49.8863

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.325	VB	0.3614	949.09076	40.40672	5.3833
2	21.817	BB	1.2179	1.66812e4	191.91763	94.6167

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.650	BB	0.4156	5442.19531	200.57816	50.0561
2	26.180	PB	1.3371	5429.98730	58.93170	49.9439

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.644	BB	0.4114	478.83350	17.96442	5.4770
2	25.664	BB	1.3563	8263.73828	84.83661	94.5230

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.432	PB	0.2874	7894.83594	423.44937	49.8306
2	19.273	BB	0.6530	7948.52832	181.72507	50.1694

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.434	VB	0.2950	740.24347	38.37048	5.1103
2	18.995	BB	0.6855	1.37450e4	293.84488	94.8897

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.287	BB	0.4489	2850.33472	98.30357	50.5350
2	23.448	BB	0.6410	2789.97827	66.48033	49.4650

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	19.287	BB	0.4887	716.32385	21.44645	5.1112
2	22.922	BB	0.7217	1.32984e4	272.73965	94.8888

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.629	BV	0.3995	435.37161	16.58025	50.0242
2	19.524	VB	0.4769	434.95074	14.07797	49.9758

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.573	VV	0.3848	373.88568	14.95781	4.4995
2	19.207	VB	0.4948	7935.65234	242.87274	95.5005

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.515	PB	1.6085	1.40597e4	130.27475	50.0430
2	40.311	BB	1.6560	1.40356e4	131.17015	49.9570

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.738	BB	1.3476	603.58844	6.07161	4.0974
2	39.993	BB	1.7070	1.41275e4	127.42570	95.9026

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.131	VV	0.2444	1.60593e4	1006.25598	49.7713
2	12.104	VV	0.2662	1.62069e4	935.48779	50.2287

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.098	VV	0.2497	4.08048e4	2487.05664	94.8434
2	12.107	VV	0.2871	2218.55444	113.10191	5.1566

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.032	PB	2.2098	1.44575e4	96.72331	49.7256
2	53.123	BB	3.7505	1.46171e4	59.27619	50.2744

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.653	VB	2.4054	1617.47388	9.61416	3.3341
2	53.934	VB	4.1160	4.68960e4	173.72986	96.6659

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	8.060	VB	0.2170	2395.61060	169.79694	30.6903
2	9.685	VB	0.2605	2374.94604	141.03963	30.4255
3	11.711	VB	0.3327	1632.73230	76.73844	20.9170
4	15.558	VB	0.4446	1402.48059	48.78475	17.9672

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	8.055	BB	0.2174	3966.37085	282.95328	92.8902
2	9.691	BP	0.2558	303.58539	18.47449	7.1098