Catalytic Asymmetric Conjugate Addition of Grignard Reagents to Coumarins – Synthesis of Versatile Chiral Building Blocks

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Supporting Information

1. General
Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60,0.25 mm. Components were visualized by UV and cerium/molybdenum staining. Progress and conversion of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI) or a LTQ Orbitrap XL (ESI). 1H, 19F and 13C NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively), a Varian VXR300 (300 and 75 MHz, respectively) or a Varian Gemini 200, using CDCl3 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl3: δ 7.26 for 1H, δ 77.0 for 13C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Enantiomeric excesses (ee values) were determined by HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10ADVP diode array detector and chiral columns as indicated. Ees were determined by comparison of the racemic mixture with the corresponding chiral compounds or the mixtures of both R and S enantiomers. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. CH2Cl2 was dried and distilled over calcium hydride, THF and Et2O were dried and distilled over Na/benzophenone. Toluene was dried and distilled over Na. MTBE was dried and distilled over CaH2. CuBr•SMe2 was purchased from Sigma-Aldrich, and used without further purification. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, n-HexMgBr, i-BuMgBr), all other Grignard reagents were prepared from the corresponding bromides with Mg in Et2O. All Grignard reagents were titrated using s-BuOH and catalytic amounts of 1,10-phenanthroline before use. L1 was prepared according to literature,1 L2-L5 were purchased from Sigma-Aldrich. All coumarins were commercially available, 3c and 3d were prepared (see below).

2.) Synthesis of starting materials

\[ \text{S1} \xrightarrow{\text{1.10 eq NaH, 2.0 eq MeI, DMF, 0 °C to r.t.}} \text{S2} \]

\[ X = \text{Cl: 99%} \quad \text{(S2a)} \]
\[ X = \text{Br: 98%} \quad \text{(S2b)} \]

\[ \text{S2} \xrightarrow{\text{1.20 eq. Ph3P, toluene, reflux}} \text{S3} \]

\[ X = \text{Cl: 90%} \quad \text{(S3a)} \]
\[ X = \text{Br: 78%} \quad \text{(S3b)} \]

\[ \text{S1} \xrightarrow{\text{2.00 eq BBr3, toluene, reflux}} \]

\[ X = \text{Cl: 77%} \quad \text{(3c)} \]
\[ X = \text{Br: 63%} \quad \text{(3d)} \]
General Procedure for the methylation of salicylic aldehydes (synthesis of S2)
The corresponding salicylic aldehyde S1 (1.00 eq.) was dissolved in DMF (Volume: 100 mL/10 mmol) and the solution cooled to 0 °C. Then, 1.00 eq. sodium hydride (as 60% suspension in mineral oil) was added slowly and the reaction mixture was stirred for 15 min at 0 °C (or until gas evolution ceased, respectively). Then, 2.00 eq. methyl iodide was added dropwise, and the reaction mixture was allowed to warm to 21 °C. When TLC showed full consumption of the starting material, the reaction was quenched by addition of water (100 mL/10 mmol). The mixture was washed with water and brine (50 mL / 10 mmol each), extracted with EtOAc (2x 50 mL / 10 mmol) and the organic phases was dried over MgSO4. The crude product was used without further purification.

5-chloro-2-methoxybenzaldehyde (S2a)

Following the general procedure for methylation of salicylic aldehydes, 2.167 g 5-chloro-2-methoxybenzaldehyde S2a (12.70 mmol, 99 % yield) was isolated as a pale yellow solid from the reaction of 5-chloro-2-hydroxybenzaldehyde (2.00 g, 12.77 mmol) with methyl iodide (1.597 ml, 25.5 mmol).

1H NMR: (400 MHz, CDCl3) δ 10.30 (s, 1H), 7.64 (s, 1H), 7.46 – 7.34 (m, 1H), 6.87 (d, J = 8.8 Hz, 1H), 3.84 (s, 3H).

13C NMR: (101 MHz, CDCl3) δ 188.12, 160.07, 135.16, 127.53, 126.00, 125.37, 113.18, 55.79.

HR-MS: (ESI+) calculated for C8H8ClO2 [M+H+] : 171.0207, found: 171.0204.

5-bromo-2-methoxybenzaldehyde (S2b)

Following the general procedure for methylation of salicylic aldehydes, 2.097 g 5-bromo-2-methoxybenzaldehyde S2b (9.75 mmol, 98 % yield) was isolated as a pale yellow solid from the reaction of 5-bromo-2-hydroxybenzaldehyde (2.00 g, 9.95 mmol) with methyl iodide (1.244 ml, 19.90 mmol).

1H NMR: (201 MHz, CDCl3) δ 10.31 (s, 1H), 7.83 (d, J = 2.6 Hz, 1H), 7.56 (dd, J = 8.9, 2.6 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 3.86 (s, 3H).

13C NMR: (50 MHz, CDCl3) δ 188.13, 160.57, 138.12, 130.70, 125.83, 113.63, 113.19, 55.82.


General procedure for the Wittig reaction of methyl 2-(triphenylphosphoranylidene)acetate with salicylic aldehydes
Salicylic aldehyde $S_2$ (1.00 eq.) was dissolved in toluene (Volume: 50 mL/10 mmol), and 1.20 eq. methyl 2-(triphenylphosphoranylidene)acetate was added to the mixture. This was heated to 110 °C until TLC showed full conversion of the starting material. After cooling, diethylether (50 mL/10 mmol) was added to precipitate any triphenylphosphinoxide, which was subsequently filtered off. All volatiles were removed under reduced pressure to give the crude products, which were purified by column chromatography (SiO$_2$, pentane/EtOAc 8:2) to yield $S_3$ as a mixture of E/Z isomers.

Methyl 3-(5-chloro-2-methoxyphenyl)acrylate ($S_{3a}$)

Following the general procedure for the Wittig reaction with salicylic aldehydes, 2.384 g methyl 3-(5-chloro-2-methoxyphenyl)acrylate $S_{3a}$ (10.52 mmol, 90 % yield) was isolated as a white solid from the reaction of 5-chloro-2-methoxybenzaldehyde $S_{2a}$ (2.00 g, 11.72 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (4.70 g, 14.07 mmol). (R$_f$ = 0.80 in pentane/EtOAc 8:2).

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 16.2$ Hz, 1H), 7.41 (d, $J = 2.6$ Hz, 1H), 7.23 (dd, $J = 8.9$, 2.6 Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 1H), 6.45 (d, $J = 16.2$ Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H).

$^{13}$C NMR: (101 MHz, CDCl$_3$) $\delta$ 167.25, 156.61, 138.50, 130.70, 129.68, 127.97, 125.57, 124.64, 119.30, 112.28, 55.62, 51.50.

HR-MS: (ESI$^+$) calculated for C$_{11}$H$_{12}$ClO$_3$ [M+H$^+$]: 227.0470, found: 227.0465.

Methyl 3-(5-bromo-2-methoxyphenyl)acrylate ($S_{3b}$)

Following the general procedure for the Wittig reaction with salicylic aldehydes, 1.977 g methyl 3-(5-bromo-2-methoxyphenyl)acrylate $S_{3b}$ (7.29 mmol, 78 % yield) was isolated as a white solid from the reaction of 5-bromo-2-methoxybenzaldehyde $S_{2b}$ (2.00 g, 9.30 mmol) with methyl 2-(triphenylphosphoranylidene)acetate (3.73 g, 11.16 mmol). (R$_f$ = 0.65 in pentane/EtOAc 8:2).

$^1$H NMR: (201 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 16.2$ Hz, 1H), 7.57 (d, $J = 2.5$ Hz, 1H), 7.39 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 6.46 (d, $J = 16.2$ Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H).

$^{13}$C NMR: (50 MHz, CDCl$_3$) $\delta$ 167.32, 156.14, 138.52, 138.49, 133.68, 130.99, 125.20, 119.39, 112.85, 112.78, 55.66, 51.61.

HR-MS: (ESI$^+$) calculated for C$_{11}$H$_{12}$BrO$_3$ [M+H$^+$]: 270.9964, found: 270.9969.
General procedure for the synthesis of coumarin derivatives 3c, 3d from methyl acrylates

According to a modified literature procedure, 1.00 eq. methyl acrylate S3 was dissolved in toluene (Volume: 50 mL / 5 mmol) and the mixture cooled to 0 °C. Then, 2.00 eq. boron tribromide was added dropwise. The reaction mixture was heated to 110 °C for 4h. After cooling to room temperature, water (50 mL / 5 mmol) was added and the aqueous layer was extracted twice with CHCl3 (30 mL / 5 mmol). After drying over MgSO4 and removal of all volatiles under reduced pressure, the crude mixture was purified by column chromatography (SiO2, pentane/EtOAc 8:2) to yield the desired coumarins 3c or 3d.

6-chloro-2H-chromen-2-one (3c)

![Image of 6-chloro-2H-chromen-2-one (3c)]

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.613 g 6-chloro-2H-chromen-2-one 3c (3.40 mmol, 77 % yield) was isolated as a pale yellow solid from the reaction of methyl 3-(5-chloro-2-methoxyphenyl)acrylate S3a (1.00 g, 4.41 mmol) with boron tribromide (0.834 ml, 8.82 mmol). (Rf = 0.75 in pentane/EtOAc 8:2).

1H NMR: (201 MHz, CDCl3) δ 7.63 (d, J = 9.6 Hz, 1H), 7.44 (dt, J = 4.9, 2.3 Hz, 2H), 7.30 – 7.18 (m, 1H), 6.44 (d, J = 9.6 Hz, 1H).
13C NMR: (50 MHz, CDCl3) δ 159.94, 152.32, 142.15, 131.65, 129.58, 127.05, 119.72, 118.20, 117.74.
HR-MS: (ESI+) calculated for C9H6ClO2 [M+H+]: 181.0051, found: 181.0051.

6-bromo-2H-chromen-2-one (3d)

![Image of 6-bromo-2H-chromen-2-one (3d)]

Following the general procedure for the synthesis of coumarin derivatives from esters, 0.522 g 6-bromo-2H-chromen-2-one 3d (2.320 mmol, 63 % yield) was isolated as an orange solid from the reaction of methyl 3-(5-bromo-2-methoxyphenyl)acrylate S3b (1.00 g, 3.69 mmol) with boron tribromide (0.697 ml, 7.38 mmol). (Rf = 0.90 in pentane/EtOAc 8:2).

1H NMR: (201 MHz, CDCl3) δ 7.68 – 7.55 (m, 3H), 7.29 – 7.15 (m, 1H), 6.45 (d, J = 9.6 Hz, 1H).
13C NMR: (50 MHz, CDCl3) δ 164.90, 159.88, 142.04, 134.54, 130.13, 120.28, 118.60, 117.83, 116.94.
HR-MS: (ESI+) calculated for C9H6BrO2 [M+H+]: 224.9546, found: 224.9548.

3. General Procedure for the asymmetric Cu-catalyzed conjugate addition of Grignard reagents to Coumarins
Copper Bromide dimethyl sulfide complex (5.0 mol %) and 5.5 mol % (R,S-Fe)-reverse Josiphos (L4) were dissolved in MTBE (Volume: 15 mL / 1 mmol substrate) and the mixture was stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and subsequently 2.5 eq. of the appropriate Grignard reagent was added. The mixture stirred for and additional 10 min at -72 °C. Then, a solution of 1.00 eq. of the appropriate coumarin 1 or 3 in MTBE (Volume: 5 mL / 1 mmol) was added dropwise over a period of 1 h. The reaction mixture was stirred until TLC showed full conversion. Then, the reaction was quenched by adding HCl solution in Et₂O (2.0 mL / 1 mmol substrate) at -72 °C. Then, 20 mL / 1 mmol saturated aqueous NH₄Cl solution was added at low temperature and the reaction mixture was allowed to warm to room temperature. Then, it was diluted with Et₂O (30 mL / 1 mmol). After washing two times with aqueous saturated NH₄Cl solution (2× 50 mL / 1 mmol) and reextraction of the aqueous layer with Et₂O (20 mL / 1 mmol), the combined organic layers were dried over MgSO₄. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO₂, EtOAc/Pentane) to yield 2 or 4.

**General Procedure for the synthesis of racemic products of the Cu-catalyzed conjugate addition to Coumarins**

1.00 eq. of the appropriate coumarin (0.485 mmol) and 30.0 mol % copper bromide dimethyl sulfide complex (0.030 g, 0.145 mmol) and 60.0 mol % triphenylphosphine (0.076 g, 0.291 mmol) were dissolved in MTBE (Volume: 15 ml), cooled to -40 °C and stirred for 10 min. Then, 2.50 eq. of the appropriate Grignard reagent (1.212 mmol) was added dropwise. The reaction mixture was stirred overnight at -40 °C. Then, the reaction was quenched by addition of 2.0 mL HCl in Et₂O (2N). Then, 20 mL saturated aqueous NH₄Cl solution was added at low temperature and the reaction mixture was allowed to warm to room temperature. Then, it was diluted with Et₂O (30 mL). After washing two times with aqueous saturated NH₄Cl solution (2x 50 mL / 1 mmol) and reextraction of the aqueous layer with Et₂O (20 mL / 1 mmol), the combined organic layers were dried over MgSO₄. All volatiles were removed under reduced pressure to give the crude product, which was purified by column chromatography (SiO₂, EtOAc/Pentane) to yield the desired compounds.

**(R)-4-ethylchroman-2-one (2a)**

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (R)-4-ethylchroman-2-one 2a (0.768 mmol, 96% yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with ethylmagnesium bromide solution (3.0 molar in Et₂O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO₂, pentane/EtOAc 10:1, Rf = 0.68 in pentane/EtOAc 10:1, 95% ee).

1H NMR: (400 MHz, CDCl₃) δ 7.29 – 7.21 (m, 1H), 7.21 – 7.15 (m, 1H), 7.11 (dd, J = 10.7, 4.2 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.78 (qd, J = 15.8, 4.9 Hz, 2H), 1.64 (tdd, J = 14.0, 11.3, 6.2 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H).
$^{13}$C NMR: (101 MHz, CDCl$_3$) $\delta$ 168.48, 151.22, 128.17, 127.84, 126.42, 124.20, 117.00, 36.52, 34.35, 27.50, 11.11.

HR-MS: (ESI$^+$) calculated for C$_{11}$H$_{12}$O$_2$Na [M+Na$^+$]: 199.0730, found: 199.0730.

$[\alpha]_D^{20} = 53.6$ (c = 1.0 in CHCl$_3$)

$[\alpha]_D^{20} = 114.6$ (c = 1.0 in C$_6$H$_6$)

The two $[\alpha]_D^{20}$ values have been used for determination of the absolute configuration by comparison with literature data.$^3, 4$

ee determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 220 nm), retention times: 8.3 min (major), 8.9 min (minor).

(R)-4-hexylchroman-2-one (2c)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.177 g (R)-4-hexylchroman-2-one 2c (0.760 mmol, 95 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with n-hexylmagnesium bromide solution (2.0 molar in Et$_2$O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.78$ in pentane/EtOAc 10:1, 99% ee).

$^1$H NMR: (201 MHz, CDCl$_3$) $\delta$ 7.30 – 6.95 (m, 4H), 3.04 – 2.87 (m, 1H), 2.81 – 2.61 (m, 2H), 1.66 – 1.45 (m, 2H), 1.44 – 1.02 (m, 8H), 0.84 (t, $J = 6.4$ Hz, 3H).

$^{13}$C NMR: (50 MHz, CDCl$_3$) $\delta$ 168.26, 151.09, 127.99, 127.65, 126.72, 124.10, 116.85, 34.94, 34.54, 34.47, 31.47, 28.94, 26.44, 22.41, 13.88.

HR-MS: (ESI$^+$) calculated for C$_{15}$H$_{20}$O$_2$Na [M+Na$^+$]: 255.1356, found: 255.1356.

$[\alpha]_D^{20} = 47.6$ (c = 1.0 in CHCl$_3$)

ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 10.5 min (minor), 12.4 min (major).

(S)-4-isopropylchroman-2-one (2d)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.145 g (S)-4-isopropylchroman-2-one 2d (0.760 mmol, 95 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with isopropylmagnesium bromide solution (1.5 molar in Et$_2$O) (1.33 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.90$ in pentane/EtOAc 10:1, 63% ee).

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 7.27 – 7.19 (m, 1H), 7.14 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.01 (d, $J = 8.1$ Hz, 1H), 2.85 (dd, $J = 10.7$, 8.9 Hz, 1H), 2.78 – 2.63 (m, 2H), 1.82 (dd, $J = 13.5$, 6.7 Hz, 1H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H).
\[^{13}\text{C}\] NMR: (101 MHz, CDCl\(_3\)) \(\delta\) 168.65, 151.46, 128.84, 128.09, 125.30, 123.87, 116.81, 41.61, 32.05, 31.96, 20.00, 19.00.

HR-MS: (ESI\(^+\)) calculated for C\(_{12}\)H\(_{15}\)O\(_2\) [M+H\(^+\)]: 191.1067, found: 191.1066.

\([\alpha]\)\(_D\)^20 = 21.6 (c = 1.0 in CHCl\(_3\))

ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 15.5 min (major), 17.2 min (minor).

(R)-4-isobutylchroman-2-one (2e)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH} & \quad \text{CH} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.118 g (R)-4-isobutylchroman-2-one 2e (0.576 mmol, 72 % yield) was isolated as a pale yellow solid from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with isobutylmagnesium bromide solution (2.0 molar in Et\(_2\)O) (1.00 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO\(_2\), pentane/EtOAc 10:1, \(R_f = 0.78\) in pentane/EtOAc 10:1, 93% ee).

\[^1\text{H}\] NMR: (400 MHz, CDCl\(_3\)) \(\delta\) 7.29 – 7.20 (m, 1H), 7.20 – 7.15 (m, 1H), 7.09 (t, \(J = 7.4\) Hz, 1H), 7.04 (d, \(J = 8.1\) Hz, 1H), 3.07 (dd, \(J = 5.3, 3.9\) Hz, 1H), 2.76 (ddd, \(J = 19.5, 15.8, 4.7\) Hz, 2H), 1.63 (dt, \(J = 13.4, 6.7\) Hz, 1H), 1.42 (dt, \(J = 21.2, 13.9, 7.5\) Hz, 2H), 0.98 (d, \(J = 6.5\) Hz, 3H), 0.89 (d, \(J = 6.6\) Hz, 3H).

\[^{13}\text{C}\] NMR: (101 MHz, CDCl\(_3\)) \(\delta\) 168.34, 151.20, 128.12, 127.48, 127.17, 124.25, 117.09, 43.62, 34.69, 32.76, 24.84, 22.59, 22.22.

HR-MS: (ESI\(^+\)) calculated for C\(_{13}\)H\(_{17}\)O\(_2\) [M+H\(^+\)]: 205.1223, found: 205.1223.

\([\alpha]\)\(_D\)^20 = 72.0 (c = 1.0 in CHCl\(_3\))

ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 13.8 min (major), 15.4 min (minor).

(R)-4-(but-3-enyl)chroman-2-one (2f)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CH} & \quad \text{CH} \\
\text{Ph} & \quad \text{CH}_2
\end{align*}
\]

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.106 g (R)-4-(but-3-en-1-yl)-3,4-dihydronaphthalen-2(1H)-one 2f (0.528 mmol, 66 % yield) was isolated as a pale yellow oil from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with butenylmagnesium bromide solution (2.38 molar in Et\(_2\)O) (0.84 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO\(_2\), pentane/EtOAc 10:1, \(R_f = 0.85\) in pentane/EtOAc 10:1, 93% ee).
$^1$H NMR: (201 MHz, CDCl$_3$) $\delta$ 7.38 – 6.93 (m, 4H), 5.93 – 5.62 (m, 1H), 5.24 – 4.83 (m, 2H), 3.10 – 2.93 (m, 1H), 2.91 – 2.61 (m, 2H), 2.25 – 1.95 (m, 2H), 1.79 – 1.55 (m, 2H).
$^{13}$C NMR: (50 MHz, CDCl$_3$) $\delta$ 168.20, 151.23, 137.18, 128.27, 127.76, 126.42, 124.26, 117.09, 115.61, 34.57, 34.28, 33.51, 30.54.
HR-MS: (ESI$^+$) calculated for C$_3$H$_4$O$_2$Na [M+Na$^+$]: 225.0886, found: 225.0884. 
$\left[\alpha\right]_D^{20} = 72.6$ (c = 1.0 in CHCl$_3$)

ee determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm), retention times: 20.4 min (minor), 21.6 min (major).

(R)-4-phenethylchroman-2-one (2g)

![Structure of 2g]

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.126 g (R)-4-phenethylchroman-2-one 2g (0.499 mmol, 73% yield) was isolated as an orange solid from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with phenylethylmagnesium bromide solution (1.50 molar in Et$_2$O) (1.14 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.65$ in pentane/EtOAc 10:1, 94% ee).

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 7.36 – 7.26 (m, 3H), 7.25 – 7.04 (m, 6H), 3.11 – 2.98 (m, 1H), 2.90 – 2.80 (m, 2H), 2.79 – 2.58 (m, 2H), 2.04 – 1.85 (m, 2H).
$^{13}$C NMR: (101 MHz, CDCl$_3$) $\delta$ 168.06, 151.17, 140.68, 128.39, 128.25, 128.14, 127.68, 126.30, 126.01, 124.23, 117.02, 35.86, 34.48, 34.35, 32.56.
HR-MS: (ESI$^+$) calculated for C$_{17}$H$_{16}$O$_2$Na [M+Na$^+$]: 275.1043, found: 275.1042. 
$\left[\alpha\right]_D^{20} = 57.0$ (c = 1.0 in CHCl$_3$)

ee determination by chiral HPLC (Chiralpak AD: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 8.3 min (minor), 9.0 min (major).

(R)-4-(4-chlorobutyl)chroman-2-one (2h)

![Structure of 2h]

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.075 g (R)-4-(4-chlorobutyl)chroman-2-one 2h (0.315 mmol, 46 % yield) was isolated as a yellow oil from the reaction of 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) with (4-chlorobutyl)magnesium bromide solution (2.30 molar in Et$_2$O) (0.744 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.65$ in pentane/EtOAc 10:1, 98% ee).
The product contains traces of dehalogenated product.

$^1$H NMR: (400 MHz, CDCl$_3$) $\delta$ 7.31 – 7.23 (m, 1H), 7.18 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.11 (td, $J = 7.4$, 1.1 Hz, 1H), 7.06 (d, $J = 8.1$ Hz, 1H), 3.52 (dt, $J = 6.5$, 5.1 Hz, 2H), 2.99 (dd, $J = 5.8$, 3.8 Hz, 1H), 2.80 (ddd, $J = 19.7$, 15.9, 4.8 Hz, 2H), 1.77 (ddd, $J = 7.7$, 6.1, 3.7 Hz, 2H), 1.68 – 1.52 (m, 4H).

$^{13}$C NMR: (101 MHz, CDCl$_3$) $\delta$ 168.20, 151.21, 128.39, 127.79, 126.33, 124.35, 117.18, 44.58, 35.10, 34.75, 33.87, 32.25, 24.05.

HR-MS: (ESI$^+$) calculated for C$_{13}$H$_{16}$O$_2$ [M+H$^+$]: 239.0833, found: 239.0842.

$[\alpha]_{D}^{20} = 84.6$ (c = 1.0 in CHCl$_3$) 
$ee$ determination by chiral HPLC (Chiralpak OD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 26.0 min (major), 27.0 min (minor).

(R)-4-ethyl-6-methylchroman-2-one (4a)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.140 g (R)-4-ethyl-6-methylchroman-2-one 4a (0.736 mmol, 92 % yield) was isolated as a pale yellow oil from the reaction of 6-methyl-2H-chromen-2-one 3a (0.128 g, 0.8 mmol) with ethylmagnesium bromide solution (3.00 molar in Et$_2$O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.85$ in pentane/EtOAc 10:1, 94% ee).

$^1$H NMR: (201 MHz, CDCl$_3$) $\delta$ 7.09 – 6.85 (m, 3H), 2.90 – 2.78 (m, 1H), 2.77 – 2.61 (m, 2H), 2.30 (s, 3H), 1.70 – 1.44 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR: (50 MHz, CDCl$_3$) $\delta$ 168.51, 149.05, 133.63, 128.50, 128.15, 126.03, 116.53, 36.42, 34.26, 27.43, 20.59, 11.00.

HR-MS: (ESI$^+$) calculated for C$_{12}$H$_{15}$O$_2$ [M+H$^+$]: 191.1067, found: 191.1067.

$[\alpha]_{D}^{20} = 19.0$ (c = 1.0 in CHCl$_3$) 
$ee$ determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 15.8 min (major), 17.3 min (minor).

(R)-4-ethyl-7-methylchroman-2-one (4b)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.141 g (R)-4-ethyl-7-methylchroman-2-one 4b (0.741 mmol, 93 % yield) was isolated as a pale yellow oil from the reaction of 7-methyl-2H-chromen-2-one 3b (0.128 g, 0.8 mmol) with ethylmagnesium bromide solution (3.00 molar in Et$_2$O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO$_2$, pentane/EtOAc 10:1, $R_f = 0.70$ in pentane/EtOAc 10:1, 97% ee).
\(^1\)H NMR: (400 MHz, CDCl\(_3\)) \(\delta 7.04\) (d, \(J = 7.7\) Hz, 1H), 6.90 (dd, \(J = 7.7, 0.8\) Hz, 1H), 6.84 (s, 1H), 2.89 – 2.81 (m, 1H), 2.74 (qd, \(J = 15.7, 4.9\) Hz, 2H), 2.31 (s, 3H), 1.59 (qt, \(J = 13.9, 7.2\) Hz, 2H), 0.93 (t, \(J = 7.4\) Hz, 3H).

\(^1\)C NMR: (101 MHz, CDCl\(_3\)) \(\delta 168.54, 151.05, 138.28, 127.47, 124.84, 123.22, 117.30, 36.09, 34.45, 27.50, 20.89, 11.00.

HR-MS: (ESI\(^+\)) calculated for C\(_{12}\)H\(_{15}\)O\(_2\) [M+H\(^+\): 191.1067, found: 191.1062.

\([\alpha]_{D}^{20} = 37.0\) (c = 1.0 in CHCl\(_3\))

**ee** determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 16.9 min (major), 18.2 min (minor).

(R)-6-chloro-4-ethylchroman-2-one (4c)

\(\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{Cl}
\end{align*}\)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.135 g (R)-6-chloro-4-ethylchroman-2-one 4c (0.641 mmol, 80 % yield) was isolated as an orange oil from the reaction of 6-chloro-2H-chromen-2-one 3c (0.144 g, 0.8 mmol), which was added as a solution in 7 mL MTBE/CH\(_2\)Cl\(_2\) (5:2), with ethylmagnesium bromide solution (3.00 molar in Et\(_2\)O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO\(_2\), pentane/EtOAc 10:1, \(R_f = 0.55\) in pentane/EtOAc 10:1, 95% ee).

\(^1\)H NMR: (300 MHz, CDCl\(_3\)) \(\delta 7.24 – 7.11\) (m, 2H), 6.95 (d, \(J = 8.5\) Hz, 1H), 2.93 – 2.83 (m, 1H), 2.82 – 2.66 (m, 2H), 1.73 – 1.47 (m, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H).

\(^1\)C NMR: (75 MHz, CDCl\(_3\)) \(\delta 167.55, 149.73, 129.16, 128.09, 127.57, 118.27, 97.86, 36.36, 33.81, 27.23, 10.91.

HR-MS: (ESI\(^+\)) calculated for C\(_{11}\)H\(_{12}\)ClO\(_2\) [M+H\(^+\): 211.0520, found: 211.0517.

\([\alpha]_{D}^{20} = 16.8\) (c = 1.0 in CHCl\(_3\))

**ee** determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 27.0 min (major), 33.1 min (minor).

(R)-6-bromo-4-ethylchroman-2-one (4d)

\(\begin{align*}
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{Br}
\end{align*}\)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.175 g (R)-6-bromo-4-ethylchroman-2-one 4d (0.686 mmol, 86 % yield) was isolated as a yellow oil from the reaction of 6-bromo-2H-chromen-2-one 3d (0.180 g, 0.8 mmol), which was added as a solution in 8 mL MTBE/CH\(_2\)Cl\(_2\) (5:3), with ethylmagnesium bromide solution (3.00 molar in Et\(_2\)O) (0.67 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO\(_2\), pentane/EtOAc 10:1, \(R_f = 0.55\) in pentane/EtOAc 10:1, 96% ee).

\(^1\)H NMR: (300 MHz, CDCl\(_3\)) \(\delta 7.41 – 7.23\) (m, 2H), 6.90 (d, \(J = 8.5\) Hz, 1H), 2.94 – 2.81 (m, 1H), 2.81 – 2.61 (m, 2H), 1.60 (td, \(J = 14.5, 7.0\) Hz, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H).
13C NMR: (50 MHz, CDCl₃) δ 167.44, 150.25, 131.04, 130.48, 128.54, 118.67, 116.68, 36.31, 33.80, 27.26, 10.93.

HR-MS: (ESI⁺) calculated for C₁₁H₁₂BrO₂ [M+H⁺]: 255.0015, found: 255.0010.

[α]D²⁰ = 5.40 (c = 1.0 in CHCl₃)

ee determination by chiral HPLC (Chiralpak OB-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 24.1 min (major), 28.4 min (minor).

(R)-4-ethyl-6,7-dimethoxychroman-2-one (4e)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.063 g (R)-4-ethyl-6,7-dimethoxychroman-2-one 4e (0.267 mmol, 55 % yield) was isolated as a brown oil from the reaction of 6,7-dimethoxy-2H-chromen-2-one 3e (0.100 g, 0.485 mmol), which was added as a solution in 5.0 mL MTBE/CH₂Cl₂ (1:1), with ethylmagnesium bromide solution (3.00 molar in Et₂O) (0.404 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO₂, pentane/EtOAc 8:2, Rf = 0.50 in pentane/EtOAc 8:2, 64% ee).

1H NMR: (201 MHz, CDCl₃) δ 6.63 (s, 1H), 6.60 (s, 1H), 3.85 (d, J = 3.3 Hz, 6H), 2.88 – 2.63 (m, 3H), 1.60 (dd, J = 13.2, 6.6 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H).

13C NMR: (50 MHz, CDCl₃) δ 168.56, 148.72, 145.46, 145.00, 117.27, 110.41, 101.28, 56.41, 56.07, 36.34, 34.49, 27.80, 11.12.

HR-MS: (ESI⁺) calculated for C₁₃H₁₇O₄ [M+H⁺]: 237.1121, found: 237.1118.

[α]D²⁰ = 20.8 (c = 1.0 in CHCl₃)

ee determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 98:2, 40 °C isotherm, 210 nm), retention times: 32.0 min (major), 44.1 min (minor).

(R)-4-ethyl-5,7-dimethoxychroman-2-one (4f)

Following the general procedure for the asymmetric Cu-catalyzed conjugate addition, 0.125 g (R)-4-ethyl-5,7-dimethoxychroman-2-one 4f (0.528 mmol, 66 % yield) was isolated as a pale yellow solid from the reaction of 5,7-dimethoxy-2H-chromen-2-one 3f (0.165 g, 0.8 mmol), which was added as a solution in 5.0 mL MTBE/CH₂Cl₂ (1:1), with ethylmagnesium bromide solution (3.00 molar in Et₂O) (0.667 ml, 2.00 mmol). The desired product was purified by column chromatography (SiO₂, pentane/EtOAc 8:2, Rf = 0.50 in pentane/EtOAc 8:2, 48% ee).

1H NMR: (201 MHz, CDCl₃) δ 6.22 (dd, J = 7.8, 2.3 Hz, 2H), 3.78 (d, J = 6.2 Hz, 6H), 3.30 – 3.08 (m, 1H), 2.71 (qd, J = 15.9, 4.1 Hz, 2H), 1.66 – 1.33 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

13C NMR: (50 MHz, CDCl₃) δ 168.64, 159.96, 157.28, 152.52, 107.63, 94.69, 93.82, 55.53, 55.42, 33.82, 30.22, 27.30, 11.03.

HR-MS: (ESI⁺) calculated for C₁₃H₁₇O₄ [M+H⁺]: 237.1121, found: 237.1121.

[α]D²⁰ = 10.6 (c = 1.0 in CHCl₃)
**ee** determination by chiral HPLC (Chiralpak OJ-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 24.0 min (major), 27.4 min (minor).

(R)-ethyl 3-(2-hydroxyphenyl)pentanoate (6)

![Chemical Structure of 6](image1.png)

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos L4 (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and the mixture was stirred at room temperature for 15 min. Then, the mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Then, a solution of 1.00 eq. 2H-chromen-2-one (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. ethanol (0.234 ml, 4.00 mmol) were added and the reaction mixture was warmed to room temperature and stirred at that temperature for 5 h. Then, the reaction was quenched by adding saturated NH4Cl solution (50 mL) and the reaction mixture was diluted with Et2O (50 mL). After separation of the organic phase it was dried over MgSO4 and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO2, pentane/EtOAc 10:1, Rf = 0.55 in pentane/EtOAc 10:1, 95% ee) to yield (R)-ethyl-3-(2-hydroxyphenyl)pentanoate 6 (0.154 g, 0.693 mmol, 87%) as a colourless oil.

1H NMR: (201 MHz, CDCl3) δ 7.19 – 6.98 (m, 3H), 6.96 – 6.82 (m, 2H), 4.30 – 3.91 (m, 2H), 3.36 (dt, J = 13.1, 7.6, 5.3 Hz, 1H), 2.70 (qd, J = 16.4, 7.3 Hz, 2H), 1.89 – 1.59 (m, 2H), 1.18 (t, J = 7.22 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H).

13C NMR: (50 MHz, CDCl3) δ 174.74, 154.14, 130.49, 127.22, 120.78, 117.03, 60.86, 40.90, 35.98, 27.77, 13.92, 12.02.

HR-MS: (ESI⁺) calculated for C13H18O3Na [M+Na⁺]: 245.1148, found: 245.1149.

[α]D²₀ = -2.0 (c = 1.0 in CHCl₃)

**ee** determination by chiral HPLC (Chiralpak AD-H: n-heptane/2-propanol 99:1, 40 °C isotherm, 210 nm), retention times: 76.2 min (minor), 80.0 min (major).

(R)-3-(2-hydroxyphenyl)-N-propylpentanamide (7)

![Chemical Structure of 7](image2.png)

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos L4 (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and the mixture was stirred at room temperature for 15 min. The mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. Next, a solution of
1.00 eq. 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. propan-1-amine (0.329 ml, 4.00 mmol) were added and the reaction mixture was warmed up to room temperature and stirred at that temperature for 16 h. The reaction was quenched by adding saturated NH₄Cl solution (50 mL) and the reaction mixture was diluted with Et₂O (50 mL). After separation of the organic phase it was dried over MgSO₄ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO₂, pentane/EtOAc 1:1; Rₜ = 0.60 in pentane/EtOAc 1:1, 96% ee) to yield (R)-3-(2-hydroxyphenyl)-N-propylpentanamide 7 (0.154 g, 0.656 mmol, 82%) as a colourless oil.

**1H NMR:** (400 MHz, CDCl₃) δ 8.71 (s (br), 1H), 7.12 – 7.02 (m, 2H), 6.94 – 6.83 (m, 2H), 6.26 (s (br), 1H), 3.34 (dd, J = 11.5, 7.3 Hz, 1H), 3.07 (dd, J = 13.3, 6.7 Hz, 2H), 2.65 (dd, J = 15.3, 4.3 Hz, 1H), 2.45 (dd, J = 14.2, 6.5 Hz, 1H), 1.72 (td, J = 7.4 Hz, 3H), 1.48 – 1.28 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H), 0.75 (t, J = 7.4 Hz, 3H).

**13C NMR:** (101 MHz, CDCl₃) δ 173.76, 154.50, 130.74, 127.19, 127.01, 120.50, 117.24, 43.32, 41.32, 36.21, 27.77, 22.33, 12.15, 11.03.

**HR-MS:** (ESI⁺) calculated for C₁₄H₂₂NO₂ [M+H⁺]: 236.1645, found: 236.1644.

**[α]D²⁰ = -38.4 (c = 1.0 in CHCl₃)**

**ee determination by chiral HPLC** (Chiralpak AB-H: n-heptane/2-propanol 95:5, 40 °C isotherm, 210 nm), retention times: 25.9 min (minor), 32.4 min (major).

(3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one (8)

In a flame-dried Schlenk tube, 2.5 mol% copper bromide dimethyl sulfide complex (4.11 mg, 0.020 mmol) and 3.0 mol% reverse Josiphos L4 (0.014 g, 0.024 mmol) were dissolved in MTBE (Volume: 10.0 ml) and stirred at room temperature for 15 min. The mixture was cooled to -72 °C and 2.5 eq. ethylmagnesium bromide solution (c = 3.0 molar, 0.800 ml, 2.4 mmol) were added and the mixture stirred for 10 more min. A solution of 1.00 eq. 2H-chromen-2-one 1 (0.117 g, 0.8 mmol) in MTBE (Volume: 5.0 ml) was added dropwise over a period of 1 h. The reaction was stirred until TLC showed full conversion to the 1,4-addition product (~2 h). Then, 5.00 eq. benzaldehyde (0.405 ml, 4.00 mmol) were added and the reaction mixture was warmed up to room temperature and stirred at that temperature for 4 h. Then, the reaction was quenched by adding saturated aq. NH₄Cl solution (50 mL) and the reaction mixture was diluted with Et₂O (50 mL). After separation of the organic phase it was dried over MgSO₄ and all volatiles were removed under reduced pressure to give the crude product as a yellow oil. This was further purified by column chromatography (SiO₂, toluene/MeOH 30:1; Rₜ = 0.45 (major), 0.35 (minor) in toluene/MeOH 30:1) to yield (3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one 8 (0.176 g, 0.624 mmol, 78%) as a colourless oil.
Product 8 was isolated as a mixture of 2 diastereomers (ratio 3:1), signals are assigned where resolved.

$^1$H NMR: (201 MHz, CDCl$_3$) $\delta$ 7.48 – 6.92 (m, 9H, major + minor), 4.59 (d, $J = 9.4$ Hz, 1H, major), 4.43 (d, $J = 10.0$ Hz, 1H, minor), 3.27 – 3.03 (m, 2H, major + minor), 2.73 (s (br), 1H, major + minor), 2.24 (t, $J = 7.3$ Hz, 1H, minor), 1.49 (qd, $J = 14.4$, 7.3 Hz, 2H, major + minor), 0.90 (t, $J = 7.3$ Hz, 3H, major), 0.77 (t, $J = 7.3$ Hz, 3H, minor).

$^{13}$C NMR: (50 MHz, CDCl$_3$) $\delta$ 168.46 (minor), 167.92 (major), 150.48 (minor), 150.45 (major), 140.77 (major), 140.47 (minor), 129.22, 128.87 (minor), 128.83 (major), 128.61 (major), 128.55 (minor), 128.36, 128.31 (minor), 128.26 (major), 128.09, 127.38, 126.80, 126.34, 125.89, 124.87, 124.32 (minor), 124.26 (major), 116.64 (minor), 116.34 (major), 72.58 (major), 64.91 (minor), 53.93 (major), 53.29 (minor), 39.70 (minor), 39.07 (major), 28.59 (major), 28.18 (minor), 11.07 (major), 10.87 (minor).

HR-MS: (ESI$^+$) calculated for C$_{18}$H$_{18}$O$_3$Na [M+Na$^+$]: 305.1148, found: 305.1149.

$[\alpha]_D^{20} = 72.4$ (c = 1.0 in CHCl$_3$)

4. References

5. NMR spectra and HPLC traces
5-chloro-2-methoxybenzaldehyde (S2a)
5-bromo-2-methoxybenzaldehyde (S2b)
Methyl 3-(5-chloro-2-methoxyphenyl)acrylate (S3a)
Methyl 3-(5-bromo-2-methoxyphenyl)acrylate (S3b)
6-chloro-2H-chromen-2-one (3c)

![Chemical Structure of 6-chloro-2H-chromen-2-one (3c)](image)

**1H NMR Spectrum**

![NMR Spectrum of 3c](image)

**13C NMR Spectrum**

![NMR Spectrum of 3c](image)
6-bromo-2H-chromen-2-one (3d)
(R)-4-ethylchroman-2-one (2a)
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(R)-4-hexylchroman-2-one (2c)
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### Results

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27
(R)-4-isobutylchroman-2-one (2e)
(R)-4-(but-3-enyl)chroman-2-one (2f)
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20.480</td>
<td>3687849</td>
<td>3.38</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>21.472</td>
<td>10552647</td>
<td>96.62</td>
</tr>
</tbody>
</table>

**Totals**

10921396 100.00
(R)-4-phenethylchroman-2-one (2g)
### Table 1: 210 nm, 8 nm

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>8.256</td>
<td>1692015</td>
<td>49.86</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>8.960</td>
<td>1701779</td>
<td>50.14</td>
</tr>
</tbody>
</table>

**Totals**

| 3393794 | 100.00 |

---

### Table 2: 210 nm, 8 nm

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>8.224</td>
<td>768520</td>
<td>2.85</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>8.917</td>
<td>26233032</td>
<td>97.15</td>
</tr>
</tbody>
</table>

**Totals**

| 27001552 | 100.00 |

---

![Graph 1](image1)

![Graph 2](image2)

![Graph 3](image3)
(R)-4-(4-chlorobutyl)chroman-2-one (2h)
### 1: 210 nm, 8 nm

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>?</td>
<td>26.208</td>
<td>2813195</td>
<td>49.65</td>
</tr>
<tr>
<td>2</td>
<td>?</td>
<td>27.157</td>
<td>2652447</td>
<td>50.35</td>
</tr>
</tbody>
</table>

**Totals**

|       | 5665642 | 100.00 |

### 2: 210 nm, 8 nm

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>?</td>
<td>25.952</td>
<td>1499105</td>
<td>98.95</td>
</tr>
<tr>
<td>2</td>
<td>?</td>
<td>26.987</td>
<td>161227</td>
<td>1.07</td>
</tr>
</tbody>
</table>

**Totals**

|       | 15099332 | 100.00 |
(R)-4-ethyl-6-methylchroman-2-one (4a)
### Table 1: Retention Time and Area Percentages

<table>
<thead>
<tr>
<th>Pk</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 15,888 Minutes</td>
<td>15,888</td>
<td>104862215</td>
<td>48.076</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 17,384 Minutes</td>
<td>17,384</td>
<td>113257593</td>
<td>51.924</td>
</tr>
</tbody>
</table>

**Totals**

|       | 218119808 | 100,000     |

### Table 2: Retention Time and Area Percentages

<table>
<thead>
<tr>
<th>Pk</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 15,792 Minutes</td>
<td>15,792</td>
<td>18631365</td>
<td>97.134</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 17,340 Minutes</td>
<td>17,340</td>
<td>490793</td>
<td>2.866</td>
</tr>
</tbody>
</table>

**Totals**

|       | 17124158 | 100,000   |
(R)-4-ethyl-7-methylchroman-2-one (4b)

3b
1. 210 nm, 2 nm

Results

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 16,800 Minutes</td>
<td>16,800</td>
<td>97583622</td>
<td>48.785</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 17,776 Minutes</td>
<td>17,776</td>
<td>102443923</td>
<td>51.215</td>
</tr>
</tbody>
</table>

Totals

|        | 200027545      | 100,000       |

Retention time: 16,800 Min

Peak name: Peak @ 16,800 Minutes

Lambda max: 204, 266

Lambda min: 261

2. 17,776 Min

Retention time: 17,776 Min

Peak name: Peak @ 17,776 Minutes

Lambda max: 204, 266

Lambda min: 261

3. 16,900 Min

Retention time: 16,900 Min

Peak name: Peak @ 16,900 Minutes

Lambda max: 204, 266

Lambda min: 261

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 16,900 Minutes</td>
<td>16,900</td>
<td>12275155</td>
<td>98.536</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 18,180 Minutes</td>
<td>18,180</td>
<td>182436</td>
<td>1.464</td>
</tr>
</tbody>
</table>

Totals

|        | 12457591        | 100,000        |
(R)-6-chloro-4-ethylchroman-2-one (4c)
### Supplementary Material (ESI) for Chemical Communications

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**Chromatogram**

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 27,364 Minutes</td>
<td>27,364</td>
<td>88081245</td>
<td>49,953</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 32,228 Minutes</td>
<td>32,228</td>
<td>88246655</td>
<td>50,047</td>
</tr>
</tbody>
</table>

**Totals**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>176327900</td>
</tr>
</tbody>
</table>

**Retention time: 27,364 Min**

Peak name: Peak @ 27,364 Minutes

Lambda max: 190, 230, 277

Lambda min: 261, 219

---

**Chromatogram**

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 32,228 Minutes</td>
<td>32,228</td>
<td>88246655</td>
<td>50,047</td>
</tr>
</tbody>
</table>

**Retention time: 32,228 Min**

Peak name: Peak @ 32,228 Minutes

Lambda max: 230, 277

Lambda min: 261, 219

---

**Chromatogram**

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 33,052 Minutes</td>
<td>33,052</td>
<td>83683117</td>
<td>97,310</td>
</tr>
</tbody>
</table>

**Totals**

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>86001439</td>
</tr>
</tbody>
</table>

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**Chromatogram**

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 27,000 Minutes</td>
<td>27,000</td>
<td>83683117</td>
<td>97,310</td>
</tr>
</tbody>
</table>

**Retention time: 27,000 Min**

Peak name: Peak @ 27,000 Minutes

Lambda max: 33, 230, 277

Lambda min: 261, 219

---

**Table**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>86001439</td>
</tr>
</tbody>
</table>
(R)-6-bromo-4-ethylchroman-2-one (4d)
### Retention Time: 25,404 Min
- **Peak name:** Peak @ 25,404 Minutes
- **Lambda max:** 229, 278, 319
- **Lambda min:** 308, 258, 217

### Retention Time: 28,392 Min
- **Peak name:** Peak @ 28,392 Minutes
- **Lambda max:** 203, 229, 278
- **Lambda min:** 307, 258, 217

---

### Table 1

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 25,404 Minutes</td>
<td>25,404</td>
<td>44806839</td>
<td>49.770</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 28,392 Minutes</td>
<td>28,392</td>
<td>45221605</td>
<td>50.230</td>
</tr>
</tbody>
</table>

**Totals**

<p>| | | | | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>90028444</td>
<td></td>
<td>100.000</td>
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</tr>
</tbody>
</table>

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### Table 2

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 24,140 Minutes</td>
<td>24,140</td>
<td>155827937</td>
<td>97.747</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 28,444 Minutes</td>
<td>28,444</td>
<td>3592045</td>
<td>2.253</td>
</tr>
</tbody>
</table>

**Totals**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>159419582</td>
<td></td>
<td>100.000</td>
<td></td>
</tr>
</tbody>
</table>
(R)-4-ethyl-6,7-dimethoxychroman-2-one (4e)
Supplementary Material (ESI) for Chemical Communications
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Chromatogram

1: 210 nm, 2 nm

Results

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 31,580 Minutes</td>
<td>31,580</td>
<td>96508099</td>
<td>46.372</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 43,188 Minutes</td>
<td>43,188</td>
<td>111608377</td>
<td>53.628</td>
</tr>
</tbody>
</table>

Totals | 208116476 | 100.000

Retention time: 31,580 Min
Peak name: Peak @ 31,580 Minutes
Lambda max: 209, 237, 285
Lambda min: 654, 353, 359

Chromatogram

Retention time: 43,188 Min
Peak name: Peak @ 43,188 Minutes
Lambda max: 209, 237, 285
Lambda min: 654, 349, 379

Chromatogram

1: 210 nm, 2 nm

Results

<table>
<thead>
<tr>
<th>Peak #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 32,008 Minutes</td>
<td>32,008</td>
<td>57728692</td>
<td>81.879</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 44,112 Minutes</td>
<td>44,112</td>
<td>127758857</td>
<td>18.121</td>
</tr>
</tbody>
</table>

Totals | 70504549 | 100.000

45
(R)-4-ethyl-5,7-dimethoxychroman-2-one (4f)
Supplementary Material (ESI) for Chemical Communications

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Chromatogram

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.568 Min</td>
<td>154537832</td>
<td>48.275</td>
</tr>
<tr>
<td>27.008 Min</td>
<td>165581498</td>
<td>51.725</td>
</tr>
</tbody>
</table>

Totals: 320119330 100.000

Retention time: 23,568 Min
Peak name: Peak @ 23,568 Minutes
Lambda max: 205, 268, 324
Lambda min: 313, 265

Retention time: 27,008 Min
Peak name: Peak @ 27,008 Minutes
Lambda max: 205, 268, 326
Lambda min: 312, 265

Chromatogram

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.004 Min</td>
<td>179332368</td>
<td>74.004</td>
</tr>
<tr>
<td>27.408 Min</td>
<td>62996163</td>
<td>25.996</td>
</tr>
</tbody>
</table>

Totals: 242328531 100.000
(R)-ethyl 3-(2-hydroxyphenyl)pentanoate (6)
Supplementary Material (ESI) for Chemical Communications
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Chromatogram

1: 210 nm, 2 nm
Results

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 76.180 MIN</td>
<td>76.180</td>
<td>16354685</td>
<td>46,807</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 80.064 MIN</td>
<td>80.064</td>
<td>11767576</td>
<td>53,193</td>
</tr>
</tbody>
</table>

Totals

Retention time: 76.180 Min
Peak name: Peak @ 76.180 Minutes
Lambda max: 203, 273, 473
Lambda min: 335, 298, 242

Chromatogram

Retention time: 80.064 Min
Peak name: Peak @ 80.064 Minutes
Lambda max: 204, 273, 473
Lambda min: 335, 298, 242

Chromatogram

1: 210 nm, 2 nm
Results

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 75.384 MIN</td>
<td>75.384</td>
<td>210098</td>
<td>2,506</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 82.012 MIN</td>
<td>82.012</td>
<td>7913271</td>
<td>97,414</td>
</tr>
</tbody>
</table>

Totals

8123369 100,000
(R)-3-(2-hydroxyphenyl)-N-propylpentanamide (7)
### Results

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
<th>Retention Time</th>
<th>Area</th>
<th>Area Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak @ 25.768 Minutes</td>
<td>25.768</td>
<td>16110380</td>
<td>54,200</td>
</tr>
<tr>
<td>2</td>
<td>Peak @ 32.564 Minutes</td>
<td>32.564</td>
<td>13613662</td>
<td>45,800</td>
</tr>
</tbody>
</table>

**Totals**

<p>| | | | | |</p>
<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>29723850</td>
<td>100,000</td>
</tr>
</tbody>
</table>

### Retention time: 25.769 Min
- Peak name: Peak @ 25.768 Minutes
- Lambda max: 205, 275, 326
- Lambda min: 305, 348, 244

### Retention time: 32.564 Min
- Peak name: Peak @ 32.564 Minutes
- Lambda max: 205, 275, 339
- Lambda min: 304, 342, 244
(3S,4R)-4-ethyl-3-(hydroxy(phenyl)methyl)chroman-2-one (8)