Nucleophilic Catalysis in the Enantioselective Synthesis of α-Methylidene-δ-lactones

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1. General methods

NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for $^1$H and 176 MHz for $^{13}$C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CDCl$_3$: 7.26 ppm for $^1$H NMR, 77.16 ppm for $^{13}$C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and [α]$_D$ values are given in deg·cm·g$^{-1}$·dm$^{-1}$; concentration c is listed in g·(100 mL)$^{-1}$. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or I$_2$ stain. Enantiomeric ratios (er) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak IA, IC and ID column). Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (Silica gel 60, 230-400 mesh, Fluka). Hydroxychalcones 1a-m were prepared according to literature procedures.$^1$ Catalysts 3a-g$^2$ were synthesized following the literature procedures.

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2. Synthesis of the acrylates 1 - general procedure

A mixture of asalicylaldehyde derivative (10 mmol), and acryloyl chloride (12 mmol) was stirred in acetone (10 ml) in the presence of K$_2$CO$_3$ (1.38 g, 10 mmol) for 24 h at room temperature. After completion of the reaction ice-cold H$_2$O (50 ml) was added to the mixture with vigorous stirring to afford a light precipitate that was filtered, washed with H$_2$O, and air-dried. Spectral data of acrylates 1a, 1c and 1d were in accordance with the literature reports.

1b (E)-5-Methyl-2-(3-oxo-3-phenylprop-1-en-1-yl)phenyl acrylate

Following the general procedure, 1b was isolated in 72% yield as an amorphous white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.92 – 7.85 (m, 3H), 7.78 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (d, J = 15.8 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.20 (dd, J = 8.1, 1.2 Hz, 1H), 6.67 (dd, J = 17.4, 1.1 Hz, 1H), 6.39 (dd, J = 17.4, 10.5 Hz, 1H), 6.08 (dd, J = 10.5, 1.1 Hz, 1H), 2.43 (s, 3H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 190.0, 164.4, 149.7, 144.0, 137.8, 135.7, 133.5, 131.3, 129.5 (2C), 128.9 (2C), 128.9, 128.0, 127.5, 126.5, 124.3, 123.3, 21.8. HRMS calculated for [C$_{19}$H$_{16}$O$_3$+H]$^+$: 293.1172; found: 293.1178.

1d (E)-2,4-Dichloro-6-(3-oxo-3-phenylprop-1-en-1-yl)phenyl acrylate

Following the general procedure, 1d was isolated in 87% yield as an amorphous light yellow solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.99 (dd, J = 8.3, 1.4 Hz, 2H), 7.70 (d, J = 15.7 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.54 – 7.48 (m, 4H), 6.72 (dd, J = 17.3, 1.0 Hz, 1H), 6.40 (dd, J = 17.3, 10.5 Hz, 1H), 6.15 (dd, J = 10.5, 1.0 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 189.6, 163.0, 145.0, 137.6, 136.0, 134.8, 133.4, 132.4, 131.6, 131.3, 129.6.

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128.9 (2C), 128.7 (2C), 126.4, 126.3, 126.0. HRMS calculated for \([C_{18}H_{22}Cl_2O_3+H]^+\): 347.0236; found: 347.0243.

1e (**E**-2-\((3\text{-Oxo-3-}(p\text{-tolyl})\text{prop-1-en-1-yl})\text{phenyl acrylate**)

Following the general procedure, 1e was isolated in 79% yield as an amorphous yellow solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.95 (d, \(J = 8.1\) Hz, 1H), 7.91 (d, \(J = 8.1\) Hz, 1H), 7.87 (d, \(J = 15.8\) Hz, 1H), 7.78 (dd, \(J = 7.8, 1.6\) Hz, 1H), 7.53 (d, \(J = 15.8\) Hz, 1H), 7.44 (td, \(J = 7.7, 1.6\) Hz, 1H), 7.31 (td, \(J = 7.7, 1.2\) Hz, 1H), 7.29 (d, \(J = 7.9\) Hz, 2H), 7.20 (dd, \(J = 8.2, 1.2\) Hz, 1H), 6.67 (dd, \(J = 17.4, 1.1\) Hz, 1H), 6.39 (dd, \(J = 17.4, 10.5\) Hz, 1H), 6.08 (dd, \(J = 10.5, 1.1\) Hz, 1H), 2.43 (s, 3H).

\(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 190.0, 164.4, 149.7, 144.0, 137.8, 135.5, 133.6, 131.3, 129.5 (2C), 128.9 (2C), 128.0, 128.0, 127.5, 126.5, 124.3, 123.3, 21.8. HRMS calculated for [C\(_{19}\)H\(_{16}\)O\(_3\)+H]^+: 293.1172; found: 293.1169.

1f (**E**-2-\((3\text{-}(4\text{-Methoxyphenyl})\text{-3-oxoprop-1-en-1-yl})\text{phenyl acrylate**)

Following the general procedure, 1f was isolated in 87% yield as an amorphous yellow solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.05–7.93 (m, 2H), 7.86 (d, \(J = 15.7\) Hz, 1H), 7.78 (dd, \(J = 7.8, 1.6\) Hz, 1H), 7.53 (d, \(J = 15.7\) Hz, 1H), 7.47–7.39 (m, 1H), 7.31 (td, \(J = 7.6, 1.2\) Hz, 1H), 7.20 (dd, \(J = 8.1, 1.2\) Hz, 1H), 6.97 (d, \(J = 8.8\) Hz, 2H), 6.67 (dd, \(J = 17.3, 1.1\) Hz, 1H), 6.39 (dd, \(J = 17.4, 10.5\) Hz, 1H), 6.08 (dd, \(J = 10.4, 1.1\) Hz, 1H), 3.88 (s, 3H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 188.4, 164.2, 163.5, 149.6, 137.2, 133.4, 131.1, 130.9, 130.8 (2C), 128.0, 127.8, 127.4, 126.4, 124.0, 123.1, 113.8 (2C), 55.5. HRMS calculated for [C\(_{19}\)H\(_{16}\)O\(_4\)+H]^+: 309.1121; found: 309.1130.

1g (**E**-2-\((3\text{-}(4\text{-Bromophenyl})\text{-3-oxoprop-1-en-1-yl})\text{phenyl acrylate**)

Following the general procedure, 1g was isolated in 89% yield as an amorphous yellow solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.94–7.82 (m, 3H), 7.77 (d, \(J = 7.8\) Hz, 1H), 7.63 (d, \(J = 8.1\) Hz, 2H), 7.52–7.40 (m, 2H), 7.32 (t, \(J = 7.6\) Hz, 1H), 7.21 (d, \(J = 8.1\) Hz, 1H), 6.67 (d, \(J = 17.3\) Hz, 1H), 6.39 (dd, \(J = 17.3, 10.5\) Hz, 1H), 6.10 (d, \(J = 10.5\) Hz, 1H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 189.3, 164.3, 149.8, 138.8, 136.9, 133.7, 132.1 (2C), 131.7, 130.2 (2C), 128.2, 128.0, 127.7, 127.5, 126.6, 123.7, 123.4. HRMS calculated for [C\(_{18}\)H\(_{13}\)BrO\(_3\)+H]^+: 357.0121; found: 357.0123.
1h (E)-2-(3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl acrylate

Following the general procedure, 1h was isolated by FC on silica (hexane/AcOEt 90:10) in 83% yield as a yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.4$ Hz, 2H), 7.87 (d, $J = 15.8$ Hz, 1H), 7.78 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.52 – 7.4 (m, 4H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.21 (dd, $J = 8.1, 1.2$ Hz, 1H), 6.67 (dd, $J = 17.4, 1.1$ Hz, 1H), 6.39 (dd, $J = 17.4, 10.5$ Hz, 1H), 6.10 (dd, $J = 10.5, 1.1$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 189.2, 164.3, 149.8, 139.5, 138.7, 136.4, 133.7, 131.6, 130.1 (2C), 129.1 (2C), 128.0, 127.7, 127.5, 126.6, 123.8, 123.4. HRMS calculated for [C$_{18}$H$_{13}$ClO$_3$+H$^+$]: 313.0626; found: 313.0622.

1i (E)-2-(3-(3-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl acrylate

Following the general procedure, 1i was isolated by FC on silica (hexane/AcOEt 90:10) in 62% yield as a yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.97 – 7.84 (m, 3H), 7.80 – 7.77 (m, 1H), 7.57 – 7.54 (m, 1H), 7.49 – 7.41 (m, 3H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 6.68 (d, $J = 17.4$ Hz, 1H), 6.40 (dd, $J = 17.4, 10.5$ Hz, 1H), 6.10 (d, $J = 10.5$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 189.1, 164.3, 149.9, 139.7, 139.1, 135.2, 133.8, 132.9, 131.7, 130.1, 128.8, 128.2, 127.6, 127.5, 126.7, 126.6, 123.7, 123.4. HRMS calculated for [C$_{18}$H$_{13}$ClO$_3$+H$^+$]: 313.0626; found: 313.0627.

1j (E)-2-(3-(2-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl acrylate

Following the general procedure, 1j was isolated by FC on silica (hexane/AcOEt 90:10) in 61% yield as a yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.72 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.54 (d, $J = 16.1$ Hz, 1H), 7.46 – 7.42 (m, 3H), 7.41 – 7.38 (m, 1H), 7.33 (td, $J = 7.4, 1.3$ Hz, 1H), 7.31 – 7.28 (m, 1H), 7.18 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.12 (d, $J = 16.1$ Hz, 1H), 6.56 (dd, $J = 17.4, 1.1$ Hz, 1H), 6.28 (dd, $J = 17.4, 10.5$ Hz, 1H), 6.02 (dd, $J = 10.5, 1.0$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 193.7, 164.1, 149.7, 139.7, 139.0, 133.4, 131.8, 131.5, 131.0, 129.5, 128.1, 128.0, 127.3, 127.3, 126.9, 126.6, 123.3. HRMS calculated for [C$_{18}$H$_{12}$ClO$_3$+H$^+$]: 313.0626; found: 313.0618.
**1k (E)-2-(3-(Naphthalen-2-yl)-3-oxoprop-1-en-1-yl)phenyl acrylate**

Following the general procedure, 1k was isolated in 82% yield as an orange solid. 

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 8.50 (dd, $J = 1.5, 0.8$ Hz, 1H), 8.08 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.99 – 7.96 (m, 1H), 7.96 – 7.91 (m, 2H), 7.89 (dd, $J = 8.1, 6.8, 1.3$ Hz, 1H), 7.57 (ddd, $J = 8.0, 6.8, 1.3$ Hz, 1H), 7.46 (ddd, $J = 8.1, 7.3, 1.6$ Hz, 1H), 7.38 – 7.32 (m, 1H), 7.22 (dd, $J = 8.1, 1.2$ Hz, 1H), 6.68 (dd, $J = 17.4, 1.1$ Hz, 1H), 6.40 (dd, $J = 17.4, 10.5$ Hz, 1H). 

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 190.2, 164.3, 149.8, 138.1, 135.6, 135.4, 133.6, 132.6, 131.4, 130.2, 129.6, 128.7, 128.6, 128.1, 128.0, 128.0, 127.5, 126.9, 126.6, 124.6, 124.4, 123.3. 

HRMS calculated for [C$_{22}$H$_{16}$O$_3$+H]$^+$: 329.1172; found: 329.1168.

**1l (E)-2-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)phenyl acrylate**

Following the general procedure, 1l was isolated in 71% yield as an amorphous yellow solid. 

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 15.8$ Hz, 1H), 7.56 (dd, $J = 15.9$ Hz, 1H), 7.42 (d, $J = 7.7, 1.6$ Hz, 1H), 7.24 (d, $J = 15.9$ Hz, 1H), 7.21 (td, $J = 7.7, 1.6$ Hz, 1H), 7.10 (d, $J = 3.6$ Hz, 1H), 7.07 (td, $J = 7.6, 1.2$ Hz, 1H), 6.98 (dd, $J = 3.6, 1.7$ Hz, 1H), 6.19 (dd, $J = 17.3, 10.5$ Hz, 1H), 5.87 (dd, $J = 10.5, 1.1$ Hz, 1H). 

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 177.5, 164.0, 153.3, 149.5, 146.6, 136.9, 133.3, 131.2, 127.8, 127.3, 127.1, 126.2, 123.1, 123.0, 117.7, 112.4. HRMS calculated for [C$_{16}$H$_{12}$O$_4$+H]$^+$: 269.0808; found: 269.0821.

**1m (E)-2-(3-Oxo-3-(Thiophen-2-yl)prop-1-en-1-yl)phenyl acrylate**

Following the general procedure, 1m was isolated in 64% yield as an yellow oil. 

$^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.91 (d, $J = 15.7$ Hz, 1H), 7.83 (dd, $J = 3.8, 1.1$ Hz, 1H), 7.78 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.69 (dd, $J = 4.9, 1.1$ Hz, 1H), 7.47 – 7.44 (m, 1H), 7.42 (d, $J = 15.6$ Hz, 1H), 7.34 – 7.30 (m, 1H), 7.21 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.18 (dd, $J = 4.9, 3.8$ Hz, 1H), 6.69 (dd, $J = 17.4, 1.0$ Hz, 1H), 6.41 (dd, $J = 17.4, 10.5$ Hz, 1H), 6.10 (dd, $J = 10.5, 1.1$ Hz, 1H). 

$^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 181.7, 164.1, 149.6, 145.3, 137.3, 134.0, 133.5, 131.9, 131.3, 128.2, 128.0, 127.5, 127.3, 126.4, 123.7, 123.2. HRMS calculated for [C$_{16}$H$_{12}$O$_3$S+H]$^+$: 285.0580; found: 285.0567.
3. Enantioselective synthesis of the α-methylidene-δ-lactones 2 via the intramolecular Rauhut-Currier reaction – screening results \[^{[a]}\]

![chemical structures](image)

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\[^{[a]}\] Reactions performed on 0.1 mmol scale (0.1 M concentration). \[^{[b]}\] Conversion as determined by \(^1\)H NMR of a crude reaction mixture. In parenthesis isolated yields are given. \[^{[c]}\] Enantiomeric ratio as determined by a chiral stationary phase HPLC. \[^{[d]}\] Concentration: 0.25 M.
An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding acrylate 1 (0.15 mmol), the catalyst 3c (0.03 mmol) and CH$_2$Cl$_2$ (0.6 mL). The reaction mixture was stirred at -25 °C and monitored by $^1$H NMR spectroscopy. When the signals of the starting acrylate 1 were no longer observed in the spectra of a crude reaction mixture it was directly subjected to FC on a silica gel to afford a target product 2.

2a (S)-3-Methylene-4-(2-oxo-2-phenylethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2a was isolated by FC on silica (CH$_2$Cl$_2$/CH$_3$OH 99:1) in 80% yield after 4 days as an amorphous white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.87 – 7.84 (m, 2H), 7.57 – 7.53 (m, 1H), 7.45 – 7.41 (m, 2H), 7.30 – 7.28 (m, 1H), 7.27 – 7.24 (m, 1H), 7.12 – 7.07 (m, 2H), 6.40 (s, 1H), 5.92 (s, 1H), 4.54 (t, $J$ = 6.6 Hz, 1H), 3.44 (dd, $J$ = 17.4, 7.2 Hz, 1H), 3.30 (dd, $J$ = 17.4, 6.1 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 196.3, 163.2, 150.6, 136.5, 135.8, 133.5, 129.8, 128.7 (2C), 128.7, 128.1 (2C), 128.0, 125.2, 124.9, 117.3, 46.0, 38.2. HRMS calculated for [C$_{18}$H$_{14}$O$_3$+H$^+$]: 279.1016; found: 279.1010.

The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 16.0 min, $\tau_{\text{minor}}$ = 14.4 min (89:11 er). [α]$^{20}_D$ = 76.2 (c = 0.5, CHCl$_3$).

2b (S)-7-Methyl-3-methylene-4-(2-oxo-2-phenylethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2b was isolated by FC on silica (CH$_2$Cl$_2$) 60% yield after 7 days as an amorphous white solid. $^1$H NMR (700 MHz, CDCl$_3$) 57.77 – 7.74 (m, 2H), 7.29 (dd, $J$ = 7.5, 1.6 Hz, 1H), 7.26 – 7.24 (m, 1H), 7.23 – 7.20 (m, 2H), 7.11 – 7.07 (m, 2H), 6.39 (s, 1H), 5.91 (s, 1H), 4.53 (t, $J$ = 6.7 Hz, 1H), 3.40 (dd, $J$ = 17.3, 7.3 Hz, 1H), 3.26 (dd, $J$ = 17.3, 6.1 Hz, 1H), 2.39 (s, 3H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 196.1, 163.4, 150.8, 144.6, 136.0, 134.2, 129.9, 129.6 (2C), 128.8, 128.3 (2C), 128.2, 125.5, 125.0, 117.4, 46.0, 38.5, 21.8. HRMS calculated for [C$_{19}$H$_{16}$O$_3$+H$^+$]: 293.1172; found: 293.1177. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}}$ = 13.0 min, $\tau_{\text{minor}}$ = 11.8 min (91:9 er). [α]$^{20}_D$ = 178.3 (c = 0.1, CHCl$_3$).
2c (S)-3-Methylene-6-nitro-4-(2-oxo-2-phenylethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2c was isolated by FC on silica (hexane/ACOEt 80:20) in 50% yield after 24 h at room temperature as an amorphous white solid. 1H NMR (700 MHz, CDCl₃) δ 8.25 (dd, J = 2.6, 0.6 Hz, 1H), 8.15 (dd, J = 8.9, 2.6 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.62 – 7.53 (m, 1H), 7.44 (dd, J = 8.3, 7.3 Hz, 2H), 7.21 (d, J = 8.9 Hz, 1H), 6.52 (s, 1H), 5.98 (s, 1H), 4.60 (t, J = 6.1 Hz, 1H), 3.59 (dd, J = 17.8, 6.1 Hz, 1H), 3.44 (dd, J = 17.8, 6.1 Hz, 1H). 13C NMR (176 MHz, CDCl₃) δ 195.5, 161.2, 155.2, 144.3, 135.9, 134.1, 133.9, 131.2, 128.8 (2C), 128.1 (2C), 126.0, 124.5, 124.2, 118.3, 46.5, 37.8. HRMS calculated for [C₁₈H₁₃NO₅⁺H˘]: 324.0866; found: 324.0866. The er was determined by HPLC using a Chiralpak IC column [hexane/i-ProOH (80:20)]; flow rate 1.0 mL/min; τmajor = 35.3 min, τminor = 37.6 min (76:24 er). [α]²⁰D = 29.5 (c = 0.9, CHCl₃).

2d (S)-6,8-Dichloro-3-methylene-4-(2-oxo-2-phenylethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2d was isolated by FC on silica (hexane/ACOEt 90:10) in 41% yield after 24 h as an amorphous light yellow solid. 1H NMR (700 MHz, CDCl₃) δ 7.88 – 7.85 (m, 2H), 7.60 – 7.56 (m, 1H), 7.45 (dd, J = 8.3, 7.4 Hz, 2H), 7.34 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 2.4, 0.6 Hz, 1H), 6.45 (s, 1H), 5.97 (s, 1H), 4.53 (t, J = 6.5 Hz, 1H), 3.45 (dd, J = 17.6, 6.7 Hz, 1H), 3.32 (dd, J = 17.6, 6.3 Hz, 1H). 13C NMR (176 MHz, CDCl₃) δ 195.5, 161.4, 145.4, 136.1, 134.4, 133.8, 130.9, 129.7, 129.2, 128.8 (2C), 128.1, 128.0 (2C), 126.5, 123.1, 45.7, 38.3. HRMS calculated for [C₁₈H₁₂Cl₂O₂⁺H˘]: 347.0236; found: 347.0249. The er was determined by HPLC using a Chiralpak ID column [hexane/i-ProOH (90:10)]; flow rate 1.0 mL/min; τmajor = 14.9 min, τminor = 16.6 min (83:17 er). [α]²⁰D = 49.4 (c = 0.4, CHCl₃).

2e (S)-3-Methylene-4-(2-oxo-2-(p-tolyl)ethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2e was isolated by FC on silica (CH₂Cl₂) in 65% yield after 10 days as an amorphous yellow solid. 1H NMR (700 MHz, CDCl₃) δ 7.76 (d, J = 8.3 Hz, 2H), 7.30 – 7.28 (m, 1H), 7.26 – 7.24 (m, 1H), 7.24 – 7.21 (m, 2H), 7.11 – 7.07 (m, 2H), 6.39 (s, 1H), 5.91 (s, 1H), 4.54 (t, J = 6.7 Hz, 1H), 3.41 (dd, J = 17.3, 7.2 Hz, 1H), 3.27 (dd, J = 17.3, 6.1 Hz, 1H), 2.39 (s, 3H). 13C NMR (176 MHz, CDCl₃) δ 195.9, 163.2, 150.6, 144.5, 135.8, 134.0, 129.7, 129.4 (2C), 128.6, 128.2 (2C), 128.1, 125.3, 124.8, 117.2, 45.8, 38.3, 21.6. HRMS calculated for [C₁₉H₁₆O₃⁺H˘]: 293.1172; found: 293.1167. The er was determined by HPLC using a Chiralpak IA column [hexane/i-ProOH (90:10)]; flow rate 1.0 mL/min; τmajor = 13.0 min, τminor = 11.8 min (82:18 er). [α]²⁰D = 74.6 (c = 0.7, CHCl₃).
(S)-4-(2-{(4-Methoxyphenyl)-2-oxoethyl})-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2f was isolated by FC on silica (CH₂Cl₂) in 45% yield after 5 days as an amorphous yellow solid. ¹H NMR (700 MHz, CDCl₃) δ 7.83 (d, J = 8.9 Hz, 2H), 7.33 – 7.17 (m, 2H), 7.15 – 6.99 (m, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.45 – 6.31 (1H), 5.90 (t, J = 6.7 Hz, 1H), 4.52 (t, J = 6.7 Hz, 1H), 3.85 (s, 3H), 3.37 (dd, J = 17.0, 7.2 Hz, 1H), 3.23 (dd, J = 17.1, 6.2 Hz, 1H). ¹³C NMR (176 MHz, CDCl₃) δ 194.7, 163.8, 163.3, 150.6, 135.8, 130.4 (2C), 129.7, 129.6, 128.6, 128.1, 125.4, 124.8, 117.2, 113.8 (2C), 55.5, 45.6, 38.4. HRMS calculated for [C₁₉H₁₆O₄⁺H]⁺: 309.1121; found: 309.1128. The er was determined by HPLC using a Chiralpak IC column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; τ_major = 26.2 min, τ_minor = 35.6 min (87:13 er). [α]²⁰₀ = 83.8 (c = 0.6, CHCl₃).

(S)-4-(2-{(4-Bromophenyl)-2-oxoethyl})-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2g was isolated by FC on silica (CH₂Cl₂) in 89% yield after 4 days as an amorphous light yellow solid. ¹H NMR (700 MHz, CDCl₃) δ 7.73 – 7.69 (m, 2H), 7.58 – 7.55 (m, 2H), 7.29 – 7.25 (m, 2H), 7.12 – 7.07 (m, 2H), 6.41 (s, 1H), 5.92 (s, 1H), 4.52 (t, J = 6.6 Hz, 1H), 3.40 (dd, J = 17.4, 7.1 Hz, 1H), 3.27 (dd, J = 17.4, 6.1 Hz, 1H). ¹³C NMR (176 MHz, CDCl₃) δ 195.3, 163.1, 150.6, 135.6, 135.1, 132.0 (2C), 129.9, 129.5 (2C), 128.8, 128.0, 124.9, 117.3, 45.9, 38.2. HRMS calculated for [C₁₉H₁₃BrO₂⁺H]⁺: 357.0121; found: 357.0128. The er was determined by HPLC using a Chiralpak IC column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; τ_major = 22.3 min, τ_minor = 32.1 min (75:25 er). [α]²⁰₀ = 73.5 (c = 0.9, CHCl₃).

(S)-4-(2-{(4-Chlorophenyl)-2-oxoethyl})-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2h was isolated by FC on silica (CH₂Cl₂) in 70% yield after 7 days as an amorphous white solid. ¹H NMR (700 MHz, CDCl₃) δ 87.81 – 7.77 (m, 2H), 7.41 – 7.38 (m, 2H), 7.29 – 7.25 (m, 2H), 7.12 – 7.08 (m, 2H), 6.40 (s, 1H), 5.92 (s, 1H), 4.52 (t, J = 6.6 Hz, 1H), 3.40 (dd, J = 17.4, 7.2 Hz, 1H), 3.27 (dd, J = 17.4, 6.1 Hz, 1H). ¹³C NMR (176 MHz, CDCl₃) δ 195.1, 163.1, 150.6, 140.1, 135.6, 134.7, 129.9, 129.4 (2C), 129.0 (2C), 128.8, 128.0, 125.0, 124.9, 117.3, 45.9, 38.2. HRMS calculated for [C₁₉H₁₃ClO₂⁺H]⁺: 313.0626; found: 313.0628. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH(90:10)]; flow rate 1.0 mL/min; τ_major = 14.0 min, τ_minor = 13.0 min (79:21 er). [α]²⁰₀ = 62.0 (c = 0.4, CHCl₃).
2i (S)-4-(2-(3-Chlorophenyl)-2-oxoethyl)-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2i was isolated by FC on silica (CH₂Cl₂) in 60% yield after 4 days as a white solid. $^1$H NMR (700 MHz, CDCl₃) δ 7.87 – 7.85 (m, 1H), 7.74 (dd, $J = 7.9, 2.1, 1.0$ Hz, 1H), 7.54 (dd, $J = 7.9, 2.1, 1.0$ Hz, 1H), 7.39 (td, $J = 7.9, 0.5$ Hz, 1H), 7.31 – 7.27 (m, 2H), 7.14 – 7.10 (m, 2H), 6.41 (s, 1H), 5.93 (s, 1H), 4.52 (t, $J = 6.6$ Hz, 1H), 3.41 (dd, $J = 17.6, 7.1$ Hz, 1H), 3.29 (dd, $J = 17.6, 6.1$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl₃) δ 195.0, 163.1, 150.6, 137.9, 135.6, 135.1, 133.5, 130.0, 128.8, 128.1, 128.0, 126.1, 124.9, 124.9, 117.3, 46.1, 38.1. HRMS calculated for [C₁₈H₁₃ClO₃]+: 313.0626; found: 313.0620. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major} = 20.4$ min, $\tau_{minor} = 19.1$ min (80:20 er). $[\alpha]^{20}_D = 108.2$ (c = 0.8, CHCl₃).

2j (S)-4-(2-(2-Chlorophenyl)-2-oxoethyl)-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2j was isolated by FC on silica (CH₂Cl₂) in 63% yield after 4 days as an amorphous white solid. $^1$H NMR (700 MHz, CDCl₃) δ 7.38 – 7.36 (m, 2H), 7.35 – 7.33 (m, 1H), 7.30 – 7.26 (m, 3H), 7.13 (td, $J = 7.5, 1.2$ Hz, 1H), 7.08 (dd, $J = 8.1, 1.2$ Hz, 1H), 6.42 (s, 1H), 5.92 (s, 1H), 4.53 (m, 1H), 3.41 (dd, $J = 17.6, 7.7$ Hz, 1H), 3.30 (dd, $J = 17.6, 6.2$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl₃) δ 199.3, 163.0, 150.6, 138.6, 135.4, 132.2, 131.0, 130.6, 129.9, 129.0, 128.8, 127.9, 127.0, 124.9, 124.8, 117.3, 50.0, 38.6. HRMS calculated for [C₁₈H₁₃ClO₃]+: 313.0626; found: 313.0631. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major} = 15.1$ min, $\tau_{minor} = 10.2$ min (92:8 er). $[\alpha]^{20}_D = 68.5$ (c = 1.5, CHCl₃).

2k (S)-3-Methylene-4-(2-(naphthalen-2-yl)-2-oxoethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2k was isolated by FC on silica (CH₂Cl₂/CH₃OH 99:1) in 63% yield after 4 days as a white solid. $^1$H NMR (700 MHz, CDCl₃) δ 8.34 (d, $J = 1.7$ Hz, 1H), 7.95 (dd, $J = 8.6, 1.7$ Hz, 1H), 7.93 – 7.90 (m, 1H), 7.86 (t, $J = 8.1$ Hz, 2H), 7.60 (dd, $J = 8.1, 6.8, 1.3$ Hz, 1H), 7.54 (dd, $J = 8.1, 6.8, 1.3$ Hz, 1H), 7.34 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.29 – 7.24 (m, 1H), 7.13 – 7.09 (m, 2H), 6.43 (s, 1H), 5.96 (s, 1H), 4.61 (t, $J = 6.6$ Hz, 1H), 3.58 (dd, $J = 17.2, 7.2$ Hz, 1H), 3.45 (dd, $J = 17.2, 6.2$ Hz, 1H). $^{13}$C NMR (176 MHz, CDCl₃) δ 196.2, 163.2, 150.6, 135.8, 135.7, 133.8, 132.4, 129.9, 129.8, 129.6, 128.7, 128.7, 128.6, 128.1, 127.7, 126.9, 125.2, 124.9, 123.5, 117.3, 46.0, 38.3. HRMS calculated for [C₂₃H₁₆O₂]+: 329.1172; found: 329.1164. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major} = 32.4$ min, $\tau_{minor} = 28.3$ min (71:29 er). $[\alpha]^{20}_D = 93.3$ (c = 1.2, CHCl₃).
2l (S)-4-(2-(Furan-2-yl)-2-oxoethyl)-3-methylenechroman-2-one (Scheme 3)

Following the general procedure, 2l was isolated by FC on silica (CH$_2$Cl$_2$) in 62% yield after 4 days as an amorphous white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.54 (d, $J = 1.6$ Hz, 1H), 7.29 – 7.22 (m, 2H), 7.13 (d, $J = 3.6$ Hz, 1H), 7.11 – 7.04 (m, 2H), 6.50 (dd, $J = 3.6$, 1.7 Hz, 1H), 6.37 (s, 1H), 5.86 (s, 1H), 4.47 (t, $J = 7.1$ Hz, 1H), 3.27 (dd, $J = 16.6$, 7.9 Hz, 1H), 3.12 (dd, $J = 16.7$, 6.4 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 185.4, 163.0, 152.4, 150.5, 146.9, 135.4, 129.9, 128.8, 128.0, 124.9, 124.9, 117.8, 117.3, 112.5, 45.6, 38.4. HRMS calculated for [C$_{16}$H$_{12}$O$_4$+H]$^+$: 269.0808; found: 269.0799. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (80:20)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 21.1$ min, $\tau_{\text{minor}} = 34.8$ min (89:11 er). $[^{10}]$$\alpha$D = 85.4 (c = 1.0, CHCl$_3$).

2m (S)-3-Methylene-4-(2-oxo-2-(thiophen-2-yl)ethyl)chroman-2-one (Scheme 3)

Following the general procedure, 2m was isolated by FC on silica (CH$_2$Cl$_2$/CH$_3$OH 99:1) in 70% yield after 7 days as an amorphous white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.64 (dd, $J = 4.9$, 1.1 Hz, 1H), 7.58 (dd, $J = 3.9$, 1.1 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.12 – 7.07 (m, 3H), 6.39 (s, 1H), 5.90 (t, $J = 0.9$ Hz, 1H), 4.50 (t, $J = 6.9$ Hz, 1H), 3.33 (dd, $J = 16.6$, 7.6 Hz, 1H), 3.21 (dd, $J = 16.6$, 6.3 Hz, 1H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 189.1, 163.1, 150.5, 143.8, 135.4, 134.5, 132.4, 130.1, 128.8, 128.3, 128.1, 125.0, 124.9, 117.3, 46.6, 38.6. HRMS calculated for [C$_{16}$H$_{12}$O$_3$S+H]$^+$: 285.0580; found: 285.0568. The er was determined by HPLC using a Chiralpak IA column [hexane/i-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 14.3$ min, $\tau_{\text{minor}} = 12.8$ min (87:13 er). $[^{10}]$$\alpha$D = 55.6 (c = 0.3, CHCl$_3$).