Supporting Information

Enantioconvergent Synthesis of Functionalized γ-Butyrolactones via (3+2)-Annulation

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**General Information:**

**Methods:** Infrared (IR) spectra were obtained using an ASI ReactIR 1000 Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on a Bruker model DRX 600 (¹H NMR at 600 MHz and ¹³C NMR at 151 MHz) spectrometer with solvent resonance as the internal standard (¹H NMR: CDCl₃ at 7.26 ppm; ¹³C NMR: CDCl₃ at 77.0 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, dt = doublet of triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Supercritical fluid chromatography (SFC) was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns as well as Regis Industries RegisPack (RP) column (φ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO₂ at the indicated percentage of methanol (MeOH) with an oven temperature of 40 °C. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Mass spectra were obtained using a Finnigan linear trap quadrapole Fourier transform (LTQ-FT) spectrometer. Samples were prepared via dilution with MeOH and doping with 0.1 M ammonium formate (MeOH). Analytical thin layer chromatography (TLC) was performed on Sorbtec 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or either aqueous potassium permanganate KMnO₄ or aqueous ceric ammonium molybdate (CAM) solution followed by heating. Product purification was accomplished using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Unless otherwise noted all reactions were carried out in flame-dried glassware with magnetic stirring. Yields and diastereomeric ratios (dr) are reported for a specific experiment and as a result may differ slightly from those found in the reported tables, which represent an average of at least two trials. In order to overlay the SFC traces for the chiral and racemic samples two separate integrations of the peaks must be taken. This results in slight discrepancies between the integration values shown in the report and seen on the trace itself.

**Materials:** NHC catalysts A,¹ D,² F,³ β-halo α-keto ester 1a,⁴ 1m,⁵ 1p-s⁶ and α,β-unsaturated aldehydes⁶ were all prepared according to literature procedures. Potassium carbonate was purchased from Sigma Aldrich and dried under vacuum (5 torr) for 3 h at 110 °C. HPLC grade chloroform (CHCl₃), ethyl acetate (EtOAc), acetonitrile (ACN), and ethanol (EtOH) were used directly from the bottle. Dichloromethane (DCM), diethyl ether (Et₂O), toluene (PhCH₃) and tetrahydrofuran (THF) were passed through a column of neutral alumina under nitrogen prior to use. Methyl tert-butyl ether (MTBE) was distilled prior to use and stored over 4 Å molecular sieves. Cinnamaldehyde was purchased from Sigma Aldrich and distilled before use. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. All racemic products were obtained via General Procedure B, using an achiral N-mesityl triazolium catalyst.⁷
The following protocol is an adaptation of a literature procedure. Under N₂, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (5.3 mmol, 1.0 equiv) and capped with a septum. To the flask, DCM (26 mL, 0.2 M) was added under an atmosphere of N₂. The septum was removed and (S)-5-isopropyl-6,6-dimethylmorpholin-3-one (5.3 mmol, 1.0 equiv) was added in a single portion. The flask was capped, put under N₂, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (5.3 mmol, 1.0 equiv) was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated in vacuo and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (26 mL, 0.2 M) and triethyl orthoformate (26.5 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (26.5 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated in vacuo. The crude residue was then purified by column chromatography using 2.5% MeOH/DCM. The resulting oil was stirred in hexanes until precipitation occurred, then filtered, providing B (1.50 g, 3.73 mmol, 71% yield) as a tan solid.

(S)-5-benzyl-2-mesityl-6,6-dimethyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium (B): Analytical data for B: ¹H NMR (600 MHz, CDCl₃) δ 8.41 (s, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.25 – 7.22 (m, 3H), 6.90 (s, 2H), 5.28 (dd, J = 11.8, 4.5 Hz, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.06 (d, J = 17.5 Hz, 1H), 3.51 (dd, J = 13.9, 4.5 Hz, 1H), 2.95 (dd, J = 14.0, 11.8 Hz, 1H), 2.29 (s, 3H), 1.81 (s, 9H), 1.59 (s, 3H), 1.47 (s, 3H); ¹³C NMR (151 MHz, CDCl₃): δ 148.7, 143.7, 142.2, 134.5, 129.7, 129.7, 129.5, 128.2, 74.0, 63.2, 56.8, 36.8, 25.0, 22.1, 21.1, 17.0; IR (thin film): 1085, 1063, 561 cm⁻¹; TLC (50% EtOAc/hexane): Rᵣ = 0.03; HRMS (ESI): Calcd. for C₂₃H₂₈BF₄N₂O: ([M+H-BF₄]⁺): 363.2305, Found: 363.2304.
Preparation of Catalyst C.

![Chemical structure]

The following protocol is an adaptation of a literature procedure. Under N₂, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (2.0 mmol, 1.0 equiv) and capped with a septum. To the flask, DCM (10 mL, 0.2 M) was added under an atmosphere of N₂. The septum was removed and (S)-5-isopropyl-6,6-diphenylmorpholin-3-one (2.0 mmol, 1.0 equiv) was added in a single portion. The flask was capped, put under N₂, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (2.0 mmol, 1.0 equiv) was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated in vacuo and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (10 mL, 0.2 M) and triethyl orthoformate (10.0 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (10.0 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 20 mL of toluene, and concentrated in vacuo. The crude residue was then purified by column chromatography using 2.5% MeOH/DCM. The resulting solid was stirred in 40% EtOAc/hexanes at 70 °C for 1 h, then filtered, providing C (0.30 g, 0.57 mmol, 29% yield) as a white solid.

(S)-5-benzyl-2-mesityl-6,6-diphenyl-5,6-dihydro-8H-[1,2,4]triazolo[3,4-c][1,4]oxazin-2-ium (C): Analytical data for C: mp 162.8-163.4 °C ¹H NMR (600 MHz, CDCl₃) δ 8.97 (s, 1H), 7.59 (m, 4H), 7.42 (t, J = 7.7 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.32 – 7.30 (m, 3H), 7.27 – 7.22 (m, 4H), 6.89 (s, 2H), 6.47 (dd, J = 10.5, 5.3 Hz, 1H), 5.40 (d, J = 17.2 Hz, 1H), 4.88 (d, J = 17.2 Hz, 1H), 3.00 – 2.92 (m, 2H), 2.29 (s, 3H), 1.72 (s, 9H); ¹³C NMR (151 MHz, CDCl₃): δ 148.9, 143.4, 142.3, 140.1, 136.9, 134.3, 130.5, 129.8, 129.7, 129.6, 129.0, 128.9, 128.1, 128.1, 127.1, 81.8, 60.5, 57.7, 37.3, 21.1, 16.7; IR (thin film): 1739, 1365, 1228, 1217, 1204, 1085, 1064 cm⁻¹; TLC (50% EtOAc/hexane): Rᵢ = 0.14; HRMS (ESI): Calcd. for C₉₅H₃₂BF₄N₃O: [M+H-BF₄]⁺: 487.2618, Found: 487.2611.
Preparation of Catalyst E.

The following protocol is an adaptation of a literature procedure. Under N₂, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (7.0 mmol, 1.0 equiv) and capped with a septum. To this flask, DCM (35 mL, 0.2 M) was added under an atmosphere of N₂. The septum was removed and (R)-5-benzylpyrrolidin-2-one (7.0 mmol, 1.0 equiv) was added in a single portion. The flask was capped, put under N₂, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (7.0 mmol, 1.0 equiv) was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated in vacuo and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (35 mL, 0.2 M) and triethyl orthoformate (35.0 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (35.0 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated in vacuo. The crude residue was stirred in EtOAc (50 mL) for 2 h then filtered, providing E (0.74 g, 1.77 mmol, 25% yield) as a tan solid.

(R)-5-benzyl-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium (E):

Analytical data for E: ¹H NMR (600 MHz, CDCl₃) δ 9.18 (s, 1H), 7.27 (m, 3H), 7.23-7.18 (m, 2H), 5.95 (s, 2H), 5.43-5.39 (m, 1H), 3.35-3.28 (m, 2H), 3.12-3.00 (m, 2H), 2.88-2.83 (m, 1H), 2.67-2.62 (m, 1H), 2.33 (s, 3H), 2.03 (s, 6H); ¹³C NMR (151 MHz, CDCl₃): δ 162.3, 141.9, 140.4, 135.0, 134.6, 129.6, 129.5, 129.0, 127.7, 61.7, 39.6, 32.0, 21.4, 21.1, 17.2; IR (thin film): 1056, 1035, 649, 633 cm⁻¹; TLC (2.5% MeOH/DCM): Rₛ = 0.13; HRMS (ESI): Calcd. for C₂₁H₂₄BF₄N₃: ([M+H-BF₄]): 318.1965, Found: 318.1966.

Preparation of Catalyst G.

Under N₂, a 50 mL flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with trimethyloxonium tetrafluoroborate (8.3 mmol, 1.0 equiv) and capped
with a septum. To the flask, DCM (40 mL, 0.2 M) was added under an atmosphere of N₂. The septum was removed and (S)-5-(((tert-butyl(dimethyl)silyl)oxy)diphenylmethyl)pyrroolid-2-one (8.3 mmol, 1.0 equiv) was added in a single portion. The flask was capped, put under N₂, and stirred vigorously for 6 h or until homogenous. Mesityl hydrazine (8.3 mmol, 1.0 equiv) was then added in a single portion and the reaction mixture was stirred for an additional 6 h. The reaction was then concentrated in vacuo and dried under high vacuum for 15 min. The crude reaction mixture was dissolved in chlorobenzene (40 mL, 0.2 M) and triethyl orthoformate (41.5 mmol, 5.0 equiv) was added. The reaction flask was equipped with a reflux condenser and heated open to the atmosphere at 135 °C for 12 h. A second portion of triethyl orthoformate (41.5 mmol, 5.0 equiv) was added and the reaction mixture was heated for an additional 24 h at 135 °C. The flask was then cooled to room temperature, diluted with 50 mL of toluene, and concentrated in vacuo. The crude residue was then purified by column chromatography using 40% EtOAc/hexanes, providing G (3.98 g, 6.52 mmol, 79% yield) as an off-white solid.

(S)-5-(((tert-butyl(dimethyl)silyl)oxy)diphenylmethyl)-2-mesityl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium (G): Analytical data for G: ¹H NMR (600 MHz, CDCl₃) δ 7.53-7.36 (m, 9H), 6.99 (s, 2H), 6.29 (d, J = 9.1 Hz, 1H), 3.38 (q, J = 10.6, 9.6 Hz, 1H), 2.87 (dd, J = 17.4, 10.3 Hz, 1H), 2.34 (s, 3H), 2.07 (s, 6H), 1.85 (s, 1H), 1.67 (s, 1H), 0.92 (s, 9H), -0.31 (s, 6H); ¹³C NMR (151 MHz, CDCl₃): δ 163.8, 142.1, 140.3, 140.0, 131.5, 129.7, 129.0, 128.5, 82.3, 29.7, 26.1, 21.1, 18.7, 17.26, 3.3, -3.5 (multiple coincident/broad resonances in the aryl region due to restricted rotation); IR (thin film): 2365, 2339, 1061, 1026, 838, 780 cm⁻¹; TLC (40% EtOAc/hexane): Rf = 0.14; LRMS (ESI): Calcd. for C₃₃H₄₂BF₄N₃O₅Si: ([M+H-BF₄]): 525.32, Found: 525.27.

General Procedure A: Preparation of α-keto esters.

\[
\begin{align*}
\text{tBuO} & \text{O} \quad \text{Cl} \\
\text{O} & \quad \text{H} \quad \text{R} \\
\text{Cl} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
1) & \text{KO}^\text{tBu}, \text{THF, } 0 \text{ °C} - \text{rt} \\
2) & (\text{Bu}_3\text{N})^+\text{Cl}^-, \text{DMC}
\end{align*}
\]

The following protocol was adopted from a literature procedure. A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with aldehyde (10.0 mmol, 1.0 equiv), tert-butyl dichloroacetate (13.0 mmol, 1.3 equiv), and THF (20 mL, 0.5 M). This solution was cooled to 0 °C and potassium tert-butoxide (13.0 mmol, 1.3 equiv) was added in one portion. The mixture was warmed slowly to room temperature and stirred for 18 h, followed by dilution with Et₂O (60 mL) and H₂O (60 mL). The layers were separated and the organic layer was further washed with H₂O (1 x 60 mL) and brine (1 x 60 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was then filtered through a short plug of SiO₂ with 15% EtOAc/hexanes, concentrated in vacuo, then dissolved in THF. To the resulting solution, tetrabutylammonium chloride (1.0 mmol, 0.10 equiv) was added in one portion. The reaction was stirred for 12 h at the indicated temperature followed by dilution with H₂O.
(60 mL). The layers were separated and the aqueous layer was further extracted with DCM (2 x 60 mL). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography using a gradient of 5-10% EtOAc/hexanes.

**tert-butyl 3-chloro-2-oxobutanoate (1n):** The title compound was prepared according to General Procedure A (stirred at rt after addition of tetrabutylammonium chloride) using acetaldehyde (0.56 mL, 10.0 mmol), affording 1n (0.95 g, 4.32 mmol, 43% yield) as a yellow oil. Analytical data for 1n: **¹H NMR** (600 MHz, CDCl₃) δ 4.99 (q, J = 6.8 Hz, 1H), 1.65 (d, J = 6.9 Hz, 3H), 1.56 (s, 9H); **¹³C NMR** (151 MHz, CDCl₃): δ 188.3, 160.2, 85.2, 54.1, 27.8, 18.7; **IR** (thin film): 2359, 2335, 1159, 668 cm⁻¹; **TLC** (5% EtOAc/hexane): R_f = 0.24; **HRMS** (ESI): Calcd. for C₈H₁₃ClO₃: ([M+Na+MeOH]): 247.0713, Found: 247.0710.

**tert-butyl 3-chloro-4-methyl-2-oxopentanoate (1o):** The title compound was prepared according to General Procedure A (stirred at 60 °C after addition of tetrabutylammonium chloride) using isobutyraldehyde (0.91 mL, 10.0 mmol), affording 1o (0.98 g, 3.95 mmol, 40% yield) as a yellow oil. Analytical data for 1o: **¹H NMR** (600 MHz, CDCl₃) δ 4.71 (d, J = 6.2 Hz, 1H), 2.42 (m, 1H), 1.56 (s, 9H), 1.05 (m, 6H); **¹³C NMR** (151 MHz, CDCl₃): δ 188.7, 160.5, 85.1, 30.7, 27.8, 27.6, 19.9, 17.9; **IR** (thin film): 1724, 1372 cm⁻¹; **TLC** (10% EtOAc/hexane): R_f = 0.11; **LRMS** (ESI): Calcd. for C₁₀H₁₇ClO₃: ([M+NH₄]): 238.12, Found: 238.27.

**Optimization data for the asymmetric homoenolate addition of 1a with (E)-PhCH=CHCHO.**
General procedure B for optimization of the asymmetric homoenoenate addition of cinnamaldehyde to 1: To a flame dried 1-dram vial was added catalyst, (0.01 mmol, 0.10 equiv) β-halo α-keto ester 1 (0.1 mmol, 1.0 equiv), solvent (0.5 mL, 0.2 M) and cinnamaldehyde (0.2 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.1 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel with Et₂O, and concentrated in vacuo. When necessary the product was purified by column chromatography using a gradient of 5-10% EtOAc/hexanes.

Ester, catalyst, base, and solvent optimization table:

| Entry | R   | X   | Cat | Solvent | Base     | conversion (%) | 2:3 | dr<sup>c</sup> | er<sup>c</sup> |
|-------|-----|-----|-----|---------|----------|---------------|-----|---------------|---------------|
| 1     | Me  | Cl  | A   | DCM     | K₂CO₃    | 100           | 6:1 | 5:1           | 75:25         |
| 2     | Me  | Cl  | B   | DCM     | K₂CO₃    | 100           | 5:1 | 3:1           | 76:24         |
| 3     | Me  | Cl  | A   | PhCH₃   | K₂CO₃    | 55            | 5.5:1 | 2:1       | --             |
| 4     | Me  | Cl  | A   | Et₂O    | K₂CO₃    | 100           | 5:1 | 3:1           | 90:10         |
| 5     | Me  | Cl  | A   | THF     | EtN/Pr₂  | 57            | 5:1 | 2:1           | 80:20         |
| 6     | Me  | Cl  | A   | THF     | DMAP<sup>a</sup> | 76       | 10:1 | 3:1       | 80:20         |
| 7     | Me  | Cl  | A   | THF     | NEt₃     | 0             | --  | --            | --             |
| 8     | Me  | Cl  | A   | THF     | TMG<sup>b</sup> | 100       | 5.5:1 | 1:1       | --             |
| 9     | Me  | Cl  | A   | Et₂O    | K₂CO₃    | 100           | >20:1 | 6:1       | 84:16         |
| 10    | tBu | Br  | A   | Et₂O    | K₂CO₃    | 100           | >20:1 | 2:1       | --             |
| 11    | tBu | Cl  | B   | Et₂O    | K₂CO₃    | 88            | >20:1 | 3:1       | 73:27         |
| 12    | tBu | Cl  | C   | Et₂O    | K₂CO₃    | 64            | 3.5:1 | 2:1       | 85:15         |
| 13    | tBu | Cl  | D   | Et₂O    | K₂CO₃    | 100           | 2:1  | 6:1         | --             |
| 14    | tBu | Cl  | E   | Et₂O    | K₂CO₃    | 100           | >20:1 | 3:1       | 78:22         |
| 15    | tBu | Cl  | F   | Et₂O    | K₂CO₃    | 100           | >20:1 | 9:1       | 93:7          |
| 16    | tBu | Br  | G   | Et₂O    | K₂CO₃    | 40            | >20:1 | >20:1      | --             |
| 17    | tBu | Cl  | G   | Et₂O    | K₂CO₃    | 100           | >20:1 | 33:1      | 99:1          |

<sup>a</sup>) 4-Dimethylaminopyridine (DMAP)  <sup>b</sup>) 1,1,3,3-Tetramethylguanidine (TMG)  <sup>c</sup>) Only reported for product 2.
General procedure B: Asymmetric (3+2)-Annulation.

\[
\begin{align*}
&\text{H} \rightarrow \text{(2.0 equiv)} \\
&\text{(±)-1} \\
&\text{G (5 mol %)} \rightarrow \text{K}_2\text{CO}_3 (1.0 equiv) \\
&\text{Et}_2\text{O (0.2 M), rt} \\
&\rightarrow \text{2} \\
&\rightarrow \text{3}
\end{align*}
\]

Method 1:
To a flame-dried 1-dram vial was added catalyst G, (0.01 mmol, 0.05 equiv) β-halo α-keto ester 1 (0.2 mmol, 1.0 equiv), Et₂O (1 mL, 0.2 M) and α,β-unsaturated aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel with Et₂O, and concentrated in vacuo. The crude product was purified by column chromatography using EtOAc/hexanes. In certain instances minor impurities remained after purification, in these cases a ¹H NMR yield utilizing mesitylene (0.20 mmol) as an internal standard is provided.

Method 2: For instances where product 2 and unreacted α,β-unsaturated aldehyde are inseparable by chromatography.
To a flame-dried 1-dram vial was added catalyst G, (0.01 mmol, 0.05 equiv) β-halo α-keto ester 1 (0.2 mmol, 1.0 equiv), Et₂O (1 mL, 0.2 M) and α,β-unsaturated aldehyde (0.4 mmol, 2.0 equiv). This solution was stirred for 5 min followed by the addition of potassium carbonate (0.2 mmol, 1.0 equiv). This reaction mixture was then stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of silica gel with Et₂O, and concentrated in vacuo. The crude product was dissolved in MeOH (1 mL) then cooled to -78 °C. NaBH₄ (5.0 equiv) was added and the reaction was stirred at -78 °C for 10 min, then quenched with saturated NH₄Cl and diluted with Et₂O (15 mL) and H₂O (10 mL). The layers were separated and the organic layer was further washed with brine (1 x 10 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography using EtOAc/hexanes.

(2R,3S)-tert-butyl 2-((R)-1-chloro-2-phenylethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2a): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester 1a (0.054 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2a (0.070 g, 0.18 mmol, 87% yield, 33:1 dr) as a white solid. The diastereomer ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.60 (minor diastereomer) and δ
4.34 (major diastereomer). Analytical data for 2a: mp 133.2-133.4 °C; 1H NMR (600 MHz, CDCl₃) δ 7.38-7.32 (m, 5H), 7.22-7.18 (m, 3H), 6.92 (dd, 2H), 4.29 (dd, J = 8.9, 3.0 Hz, 1H), 3.88 (dd, J = 11.4, 2.0 Hz, 1H), 3.17 (dd, J = 14.5, 2.0 Hz, 1H), 3.09 (dd, J = 17.9, 8.8 Hz, 1H), 2.82 (dd, J = 18.0, 3.0 Hz, 1H), 2.75 (dd, J = 14.5, 11.5 Hz, 1H), 1.61 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.8, 167.5, 136.9, 136.4, 129.2, 128.9, 128.6, 128.4, 128.2, 126.8, 90.3, 84.6, 62.0, 46.7, 38.9, 36.1, 27.9; IR (thin film): 2360, 2339, 1794, 1515, 1369, 1229, 1216 cm⁻¹; TLC (10% EtOAc/hexane): Rₜ = 0.01; HRMS (ESI): Calcd. for C₂₃H₂₅ClO₅: ([M+NH₄]⁺): 418.1784; Found: 418.1785; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, λ = 210 nm, Rₜ (major) = 6.3 min Rₜ (minor) = 10.2 min, 99:1 er; [α]₀ = +18.6 (c = 0.01, DCM).

(2R,3S)-tert-butyl 2-((R)-1-chloro-2-phenylethyl)-3-(4-methoxyphenyl)-5-oxotetrahydrofuran-2-carboxylate (2b): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester 1a (0.054 g, 0.20 mmol), and (E)-3-(4-methoxyphenyl)acrylaldehyde (0.066 g, 0.40 mmol) affording 2b (0.052 g, 0.12 mmol, 60% yield, 49:1 dr) as a colorless oil. The diastereomer ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.59 (minor diastereomer) and δ 4.35 (major diastereomer). Analytical data for 2b: 1H NMR (600 MHz, CDCl₃) δ 7.24-7.17 (m, 4H), 6.97-6.96 (m, 2H), 6.89-6.86 (m, 2H), 4.24 (dd, J = 8.8, 2.9 Hz, 1H), 3.84 (dd, J = 11.3, 2.1 Hz, 1H), 3.79 (s, 3H), 3.20 (dd, J = 14.5, 2.0 Hz, 1H), 3.07 (dd, J = 17.9, 8.9 Hz, 1H), 2.80-2.71 (m, 2H). 1.60 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.9, 167.6, 159.5, 137.1, 129.8, 129.3, 128.3, 126.8, 114.2, 90.5, 84.5, 62.1, 55.3, 46.1, 39.1, 36.4, 28.0 (two coincident resonances); IR (thin film): 1794, 1735, 1515, 1369, 1229, 1216 cm⁻¹; TLC (10% EtOAc/hexane): Rₜ = 0.01; HRMS (ESI): Calcd. for C₂₄H₂₇ClO₅: ([M+NH₄]⁺):448.1891; Found: 448.1890; SFC OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, Rₜ (major) = 7.6 min Rₜ (minor) = 12.0 min, 99:1 er; [α]₀ = +3.9 (c = 0.01, DCM).

2R,3S)-tert-butyl 2-((R)-1-chloro-2-phenylethyl)-3-(4-chlorophenyl)-5-oxotetrahydrofuran-2-carboxylate (2c): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester 1a (0.054 g, 0.20 mmol), and (E)-3-(4-chlorophenyl)acrylaldehyde (0.066 g, 0.40 mmol) affording 2c (0.060 g, 0.14 mmol, 69% yield, 34:1 dr) as a colorless oil. The diastereomer ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.55 (minor diastereomer) and δ 4.38 (major...
diastereomer). Analytical data for 2c: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.30 (m, 2H), 7.27-7.20 (m, 5H), 7.00 (d, \(J = 7.0\) Hz, 2H), 4.28 (dd, \(J = 8.7, 2.6\) Hz, 1H), 3.76 (dd, \(J = 11.4, 2.0\) Hz, 1H), 3.29 (dd, \(J = 14.6, 2.0\) Hz, 1H), 3.09 (dd, \(J = 20.8, 11.4\) Hz, 1H), 2.79-2.71 (m, 2H), 1.61 (s, 9H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 174.4, 167.1, 136.8, 135.2, 134.4, 130.0, 129.1, 129.8, 127.0, 90.1, 84.8, 61.7, 46.3, 39.3, 36.5, 35.0; IR (thin film): 1795, 1735, 1515, 1368, 1228, 1217 cm\(^{-1}\); TLC (10% EtOAc/hexane): \(R_f = 0.26\); HRMS (ESI): Calcd. for \(\text{C}_{22}\text{H}_{24}\text{ClO}_4\): \([\text{M}+\text{NH}_4]^+\): 452.1396; Found: 452.1395; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, \(\lambda = 210\) nm, \(t_R\) (major) = 4.8 min \(t_R\) (minor) = 7.1 min, 97.5:2.5 er; \([\alpha]_D^\ominus = +2.4\) (c = 0.008, DCM).

![Diagram of compound 2d](image)

\((2R,3S)-\text{ tert-butyl}\ 2-((\text{R})-1\text{-chloro-2-phenylethyl})\text{-5-oxo-3-(p-tolyl)tetrahydrofuran-2-carboxylate (2d):}\) The title compound was prepared according to General Procedure B (Method 1) using \(\alpha\)-keto ester 1a (0.054 g, 0.20 mmol), and (E)-3-(p-tolyl)acrylaldehyde (0.58 g, 0.40 mmol) affording 2d (0.062 g, 0.15 mmol, 73% yield, 43:1 dr) as a colorless oil. The diastereomer ratio was determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \(\delta 4.61\) (minor diastereomer) and \(\delta 4.31\) (major diastereomer). Analytical data for 2d: \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.23-7.16 (m, 7H), 6.96-6.94 (m, 2H), 4.25 (dd, \(J = 8.8, 2.9\) Hz, 1H), 3.88 (dd, \(J = 11.4, 2.0\) Hz, 1H), 3.19 (dd, \(J = 14.5, 2.1\) Hz, 1H), 3.08 (dd, \(J = 17.9, 8.9\) Hz, 1H), 2.81-2.74 (m, 2H), 2.34 (s, 3H), 1.61 (s, 9H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 174.9, 167.6, 138.2, 137.1, 133.4, 129.6, 129.3, 128.5, 128.2, 126.8, 90.4, 84.5, 62.0, 46.5, 39.0, 36.2, 27.93, 21.0; IR (thin film): 1795, 1735, 1369, 1228, 1216 cm\(^{-1}\); TLC (10% EtOAc/hexane): \(R_f = 0.27\); HRMS (ESI): Calcd. for \(\text{C}_{24}\text{H}_{27}\text{ClO}_4\): \([\text{M}+\text{NH}_4]^+\): 432.1942; Found: 432.1941; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, \(\lambda = 210\) nm, \(t_R\) (major) = 6.0 min \(t_R\) (minor) = 9.7 min, 97.5:2.5 er; \([\alpha]_D^\ominus = +9.4\) (c = 0.02, DCM).

![Diagram of compound 2e](image)

\((2R,3S)-\text{ tert-butyl}\ 2-((\text{R})-1\text{-chloro-2-phenylethyl})\text{-5-oxo-3-(m-tolyl)tetrahydrofuran-2-carboxylate (2e):}\) The title compound was prepared according to General Procedure B (Method 1) using \(\alpha\)-keto ester 1a (0.054 g, 0.20 mmol), and (E)-3-(m-tolyl)acrylaldehyde (0.58 g, 0.40 mmol) affording 2e (0.062 g, 0.15 mmol, 73% yield, 32:1 dr) as a white solid. The diastereomer ratio was determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \(\delta 4.60\) (minor diastereomer) and \(\delta 4.30\) (major diastereomer). Analytical data for 2e: mp 116.0-116.6 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.28-7.12 (m, 7H), 6.93-6.92 (m, 2H), 4.25 (dd, \(J = 8.9, 3.1\) Hz, 1H), 3.93 (dd, \(J = 11.4, 2.0\) Hz, 1H), 3.15 (dd, \(J =
14.5, 2.0 Hz, 1H), 3.08 (dd, J = 18.0, 8.9 Hz, 1H), 2.82 (dd, J = 18.0, 3.1 Hz, 1H), 2.76 (dd, J = 14.5, 11.4 Hz, 1H), 2.35 (s, 3H), 1.62 (s, 9H); \[^{13}C\] NMR (151 MHz, CDCl\(_3\)): \(\delta\) 174.8, 167.6, 138.7, 137.1, 136.4, 129.4, 129.2, 129.2, 128.8, 128.2, 126.8, 125.5, 90.4, 84.5, 62.1, 46.8, 38.9, 36.0, 27.9, 21.4; IR (thin film): 1795, 1734, 1369, 1158, 839, 750, 699 cm\(^{-1}\); TLC (10% EtOAc/hexane): \(R_f = 0.24\); HRMS (ESI): Calcd. for C\(_{24}\)H\(_{27}\)ClO\(_4\)·(\([\text{M}+\text{NH}_4]\))): 432.1942, Found: 432.1940; SFC OD, 5% MeOH, flow rate = 3.0 mL/min, \(\lambda = 210\) nm, \(t_R\) (major) = 4.1 min \(t_R\) (minor) = 6.7 min, 98.5:1.5 er; \([\alpha]_D = +16.7\) (c = 0.03, DCM).

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\text{(2R,3S)-tert-butyl 2-((R)-1-chloro-2-phenylethyl)-5-oxo-3-(thiophen-2-yl)tetrahydrofuran-2-carboxylate (2i): The title compound was prepared according to General Procedure B (Method 1) using \(\alpha\)-keto ester 1a (0.054 g, 0.20 mmol), and (E)-3-(thiophen-2-yl)acrylaldehyde (0.055 g, 0.40 mmol) affording 2i (0.069 g, 0.17 mmol, 85% yield, 50:1 dr) as a white solid. The diastereomer ratio was determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \(\delta\) 4.38 (minor diastereomer) and \(\delta\) 4.27 (major diastereomer). Analytical data for 2i: mp 161.8-162.1 \(^\circ\)C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.34 (d, \(J = 5.1\) Hz, 1H), 7.25-7.20 (m, 3H), 7.13 (d, \(J = 3.5\) Hz, 1H), 7.05 (dd, \(J = 5.1, 3.6\) Hz, 1H), 6.91 (d, \(J = 6.5\) Hz, 2H), 4.54 (dd, \(J = 9.1, 6.0\) Hz, 1H), 4.20 (dd, \(J = 11.5, 2.0\) Hz, 1H), 3.20-3.13 (m, 1H), 3.15-3.09 (m, 1H), 2.98 (dd, \(J = 17.9, 6.0\) Hz, 1H), 2.72 (m, 1H), 1.61 (s, 9H); \[^{13}C\] NMR (151 MHz, CDCl\(_3\)): \(\delta\) 173.2, 167.2, 137.9, 136.8, 129.2, 128.3, 127.4, 127.3, 126.9, 125.9, 89.8, 84.9, 62.7, 42.4, 38.6, 36.6, 27.9; IR (thin film): 1796, 1751, 1369, 1158, 755, 700 cm\(^{-1}\); TLC (10% EtOAc/hexane): \(R_f = 0.18\); HRMS (ESI): Calcd. for C\(_{22}\)H\(_{23}\)ClO\(_4\)·(\([\text{M}+\text{NH}_4]\))): 424.1350, Found: 424.1348; SFC OD, 10% MeOH, flow rate = 3.0 mL/min, \(\lambda = 210\) nm, \(t_R\) (major) = 3.7 min \(t_R\) (minor) = 8.5 min, 99.5:0.5 er; \([\alpha]_D = +24.0\) (c = 0.03, DCM).

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(2R,3S)-tert-butyl 2-((R)-1-chloro-2-phenylethyl)-3-(furan-2-yl)-5-oxotetrahydrofuran-2-carboxylate (2j): The title compound was prepared according to General Procedure B (Method 2) using \(\alpha\)-keto ester 1a (0.045 g, 0.20 mmol), and (E)-3-(furan-2-yl)acrylaldehyde (0.049 g, 0.40 mmol) affording 2j (0.070 g, 0.18 mmol, 89% yield, 6:1 dr) as a white solid. The diastereomer ratio was determined by \(^1\)H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \(\delta\) 4.26 (minor diastereomer) and \(\delta\) 4.06 (major diastereomer). Analytical data for 2j: mp 143.2-144.0 \(^\circ\)C; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.46 (d, \(J = 1.8\) Hz, 1H), 7.27-7.20 (m, 3H), 7.03 (dd, \(J = 6.8, 1.7\) Hz, 2H),...
6.42-6.40 (m, 2H), 4.33 (dd, J = 8.3, 6.2 Hz, 1H), 4.00 (dd, J = 11.5, 2.1 Hz, 1H), 3.08 (dd, J = 14.4, 2.1 Hz, 1H), 2.99 (m, 2H), 2.74 (m, 1H), 1.58 (s, 9H); \( ^{13}C\) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 173.4, 167.0, 149.1, 142.8, 136.9, 129.2, 128.3, 126.9, 111.0, 110.2, 89.8, 84.6, 62.8, 40.9, 38.4, 33.4, 27.9; \( \text{IR} \) (thin film): 1797, 1735, 1370, 1155, 1133 cm\(^{-1}\); TLC (10% EtOAc/hexane): \( R_f = 0.12; \) HRMS (ESI): Calcd. for C\(_{21}\)H\(_{23}\)ClO\(_5\): ([M+NH\(_4\)]): 408.1578, Found: 408.1576; SFC OD, 3.9% MeOH, flow rate = 3.0 mL/min, \( \lambda = 210 \) nm, \( t_R \) (major) = 4.3 min \( t_R \) (minor) = 9.7 min, 96:4 er; [\( \alpha \)]\(_D\) = +25.9 (c = 0.02, DCM).

\( (2R,3S)\)-tert-butyl -2-((R)-1-chloro-2-phenylethyl)-5-oxo-3-((E)-styryl)tetrahydrofuran-2-carboxylate (2k): The title compound was prepared according to General Procedure B (Method 1) using \( \alpha \)-keto ester 1a (0.054 g, 0.20 mmol), and \( (2E,4E)\)-5-phenylpent-2,4-dienal (0.063 g, 0.20 mmol) affording 2k (0.067 g, 0.15 mmol, 74% yield, 40:1.5:1 dr) as a white solid. The diastereomer ratio was determined by \( ^{1}H\) NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \( \delta \) 4.75 (minor diastereomer), \( \delta \) 4.62 (minor diastereomer), and \( \delta \) 4.41 (major diastereomer). Analytical data for 2k: mp 133.2-133.4 °C; \( ^{1}H\) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.40-7.34 (m, 4H), 7.31-7.22 (m, 4H), 7.16-7.15 (m, 2H), 6.67 (d, \( J = 15.9 \) Hz, 1H), 6.33 (dd, \( J = 15.9, 7.9 \) Hz, 1H), 4.32 (dd, \( J = 11.5, 2.0 \) Hz, 1H), 3.82 (q, \( J = 7.8 \) Hz, 1H), 3.31 (dd, \( J = 14.3, 2.0 \) Hz, 1H), 2.95-2.86 (m, 2H), 2.74 (dd, \( J = 17.9, 6.5 \) Hz, 1H), 1.58 (s, 9H); \( ^{13}C\) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 173.7, 167.3, 136.6, 135.7, 135.1, 129.3, 128.8, 128.5, 128.4, 127.1, 126.4, 122.9, 89.7, 84.4, 63.2, 44.7, 39.0, 34.5, 27.9; \( \text{IR} \) (thin film): 1796, 1735, 1370, 1197, 1157, 1133, 749, 700 cm\(^{-1}\); TLC (10% EtOAc/hexane): \( R_f = 0.14; \) HRMS (ESI): Calcd. for C\(_{25}\)H\(_{27}\)ClO\(_4\): 444.1942, Found: 444.1946; SFC Regis RP, 2.5% MeOH, flow rate = 1.5 mL/min, \( \lambda = 210 \) nm, \( t_R \) (major) = 13.4 min \( t_R \) (minor) = 16.3 min, 97:3 er; [\( \alpha \)]\(_D\) = -48.6 (c = 0.03, DCM).

\( (2R,3S)\)-tert-butyl -2-((R)-1-chloro-2-phenylethyl)-5-oxo-3-((E)-styryl)tetrahydrofuran-2-carboxylate (2l): The title compound was prepared according to General Procedure B (Method 1) using \( \alpha \)-keto ester 1a (0.045 g, 0.20 mmol), and \( (E)\)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2l (0.052 g mix of diastereomers + aldehyde dimerization, 43% \( ^{1}H\) NMR yield, >20:1 dr) as a colorless oil. The diastereomer ratio was determined by \( ^{1}H\) NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \( \delta \) 4.77 (minor diastereomer) and \( \delta \) 4.55 (major diastereomer). Analytical
data for 2l: 1H NMR (600 MHz, CDCl₃) major diastereomer: δ 7.36-7.23 (m, 5H), 4.50 (dd, J = 11.4, 2.1 Hz, 1H), 4.30-4.19 (m, 2H), 3.79-3.75 (m, 1H), 3.39 (dd, J = 14.2, 2.0 Hz, 1H), 2.91-2.82 (m, 3H), 1.56 (s, 9H), 1.29-1.24 (m, 3H); minor diastereomer: δ 7.36-7.23 (m, 5H), 4.73 (dd, J = 11.2, 2.3 Hz, 1H), 4.30-4.19 (m, 2H), 3.57 (dd, J = 14.6, 2.3 Hz, 1H), 3.20 (dd, J = 18.0, 10.4 Hz, 1H), 2.91-2.82 (m, 3H), 1.50 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H); 13C NMR major diastereomer (151 MHz, CDCl₃): δ 172.5, 169.9, 166.3, 136.8, 129.4, 128.5, 127.1, 87.9, 84.9, 62.2, 61.9, 46.3, 39.2, 32.9, 27.9, 14.0; IR (thin film): 1800, 1734, 1369, 1259, 1197, 1153, 750 cm⁻¹; TLC (10% EtOAc/hexane): Rf = 0.30; HRMS (ESI): Calcd. for C₂₀H₂₅ClO₆· ([M+NH₄]⁺): 414.1684, Found: 414.1700; SFC Regis OD, 2-8% MeOH gradient, linear ramp rate, flow rate = 1.5 mL/min, λ = 210 nm, tᵣ (major) = 8.9 min tᵣ (minor) = 12.3 min, 94:6 er; [α]D = +14.4 (c = 0.03, DCMS).

Synthesis of (2R,3S)-tert-butyl 2-((R)-chloro(phenyl)methyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2m) and (2R)-2-(tert-butoxy)-2-((R)-chloro(phenyl)methyl)-5-phenylidihydrofuran-3(2H)-one (3m): The title compounds were prepared according to General Procedure B (Method 1) using α-keto ester 1m (0.051 g, 0.20 mmol), (E)-cinnamaldehyde (0.04 mL, 0.40 mmol), and THF as the solvent (1.0 mL, 0.2 M) affording both the major and minor diastereomers of 2m major (0.036 g, 0.09 mmol, 47% yield, >30:1 dr) and 2m minor (0.020 g, 0.05 mmol, 26% yield) in a 1.5:1 ratio as white solids.

The diastereomeric ratio of 2m was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.47 (minor diastereomer), and δ 4.79 (major diastereomer). Analytical data for 2m major: mp 153.8-154.0 °C; 1H NMR (600 MHz, CDCl₃) δ 7.58 (d, J = 7.0 Hz, 2H), 7.47-7.39 (m, 5H), 7.27-7.26 (m, 3H), 4.74 (s, 1H), 3.98 (dd, J = 12.4, 9.9 Hz, 1H), 3.50 (dd, J = 17.6, 12.4 Hz, 1H), 2.92 (dd, J = 17.6, 10.0 Hz, 1H), 1.14 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.2, 167.3, 137.5, 133.1, 129.5, 129.0, 128.9, 128.7, 128.6, 128.4, 89.3, 84.0, 63.2, 49.2, 34.1, 27.3; IR (thin film): 2364, 2341, 1796, 1753, 1369, 1125, 700 cm⁻¹; TLC (10% EtOAc/hexane): Rf = 0.15; HRMS (ESI): Calcd. for C₂₀H₂₅ClO₆· ([M+NH₄]⁺): 404.1629, Found: 404.1627; SFC OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, tᵣ (major) = 5.0 min tᵣ (minor) = 6.9 min, 97:3 er; [α]D = +76.5 (c = 0.01, DCMS).

Analytical data for 2m minor: mp 109.8-110.2 °C 1H NMR (600 MHz, CDCl₃) δ 7.55-7.53 (m, 2H), 7.39-7.27 (m, 8H), 5.41 (s, 1H), 4.33 (t, J = 9.6 Hz, 1H), 3.13 (dd, J = 17.7, 9.3 Hz, 1H), 3.06 (dd, J = 17.7, 9.7 Hz, 1H), 0.77 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.4, 165.3, 137.0, 136.0, 129.2, 129.1, 128.9, 128.5, 128.4, 128.2, 91.2, 84.0, 64.4, 48.0, 34.0, 26.9; IR (thin film): 1735, 1365, 1228, 1217, 529, 519 cm⁻¹; TLC (10% EtOAc/hexane): Rf = 0.22; HRMS (ESI): Calcd. for C₂₀H₂₅ClO₆· ([M+NH₄]⁺): 404.1629,
Found: 404.1627; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, \( \lambda = 210 \) nm, \( t_R \) (major) = 6.8 min \( t_R \) (minor) = 8.9 min, 95:5 er; [\( \alpha \)]D = -11.6 (c = 0.01, DCM).

\[ (2R,3S)\text{-}t\text{-}bu \]

2-((R)-1-chloroethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2n): The title compound was prepared according to General Procedure B (Method 2) using \( \alpha \)-keto ester 1n (0.038 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2n (0.032 g 4:1 mix of isomers, 52% \( ^1H \) NMR yield) as a colorless oil. The isomer ratio was determined by \( ^1H \) NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \( \delta = 5.45 \) (minor product), and \( \delta = 4.25 \) (major product) in conjunction with the resonances at \( \delta = 1.77 \) (minor product), and \( \delta = 1.43 \) (major product). Analytical data for 2n: \( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta = 7.37-7.34 \) (m, 3H), 7.29-7.26 (m, 2H), 4.22 (dd, \( J = 8.7, 2.7 \) Hz, 1H), 3.34 (q, \( J = 6.7 \) Hz, 1H); 3.03 (dd, \( J = 17.9, 8.7 \) Hz, 1H), 2.74 (dd, \( J = 17.9, 2.7 \) Hz, 1H), 1.57 (s, 9H), 1.40 (d, \( J = 6.7 \) Hz, 3H); \( ^13C \) NMR (151 MHz, CDCl\(_3\)); \( \delta = 147.9, 167.5, 128.8, 128.7, 128.1, 98.4, 84.4, 55.4, 46.8, 36.4, 27.9, 20.0; IR (thin film): 2363, 1792, 1734, 1457, 1369, 1228, 1205, 1134 cm\(^{-1}\); TLC (10% EtOAc/hexane): \( R_f = 0.22 \); HRMS (ESI): Calcd. for C\(_{17}\)H\(_{21}\)ClO\(_4\): ([M+NH\(_4\)]): 342.1472, Found: 342.1469; SFC OD, 2.5% MeOH, flow rate = 1.5 mL/min, \( \lambda = 210 \) nm, \( t_R \) (major) = 2.3 min \( t_R \) (minor) = 2.7 min, 97:3 er; [\( \alpha \)]D = +19.0 (c = 0.008, DCM).

\[ (2R,3S)\text{-}t\text{-}bu \]

 tert-butyl-2-((R)-fluoro(phenyl)methyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2p): The title compound was prepared according to General Procedure B (Method 1) using \( \alpha \)-keto ester 1p (0.048 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2p (0.055 g, 0.15 mmol, 74% yield, 4:1 dr) as a white solid. The diastereomer ratio was determined by \( ^1H \) NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at \( \delta = 5.94 \) (minor diastereomer) and \( \delta = 5.43 \) (major diastereomer). Analytical data for 2p: mp 98.8-99.4 °C; \( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta = 7.48-7.39 \) (m, 8H), 7.33-7.29 (m, 2H), 2.61 (d, \( J = 43.3 \) Hz, 1H), 3.93 (dd, \( J = 12.6, 9.4 \) Hz, 1H), 3.37-3.32 (m, 1H), 2.93-2.88 (m, 1H), 1.26 (s, 9H); \( ^13C \) NMR (151 MHz, CDCl\(_3\)); \( \delta = 147.4, 167.6, 128.8, 128.7, 128.1, 98.4, 55.3, 46.8, 36.4, 27.9, 20.0; IR (thin film): 1797, 1756, 1130, 768, 521 cm\(^{-1}\); TLC (10% EtOAc/hexane): \( R_f = 0.08 \); LRMS (ESI): Calcd. for C\(_{22}\)H\(_{23}\)F \(_2\)O\(_4\): ([M+NH\(_4\)]): 388.19, Found: 388.31; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, \( \lambda = 210 \) nm, \( t_R \) (major) = 5.3 min \( t_R \) (minor) = 6.7 min, 97:3 er; [\( \alpha \)]D = +42.1 (c = 0.02, DCM).
(2R,3S) tert-butyl -2-((R)-1-chlorobut-3-en-1-yl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2q): The title compound was prepared according to General Procedure B (Method 1) using α-keto ester 1q (0.044 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2q (0.053 g, 0.15 mmol, 76% yield, 11:1 dr) as a white solid. The diastereomer ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.46 (minor diastereomer) and δ 4.28 (major diastereomer). Analytical data for 2q: mp 120.0-120.6 ºC; 1H NMR (600 MHz, CDCl₃) δ 7.37-7.33 (m, 3H), 7.28-7.27 (m, 2H), 5.64-5.57 (m, 1H), 5.01-4.93 (m, 2H), 4.24 (d, J = 7.8 Hz, 1H), 3.64 (d, J = 11.1 Hz, 1H), 3.03 (dd, J = 17.8, 8.7 Hz, 1H), 2.75-2.72 (m, 1H), 2.59-2.55 (m, 1H), 2.35-2.29 (m, 1H), 1.57 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.8, 167.35, 136.7, 133.4, 128.8, 128.6, 128.4, 118.2, 90.3, 84.5, 60.0, 46.9, 37.4, 36.3, 27.9; IR (thin film): 2979, 1731, 1246, 1152, 1126, 698 cm⁻¹; TLC (10% EtOAc/hexane): Rᵣ = 0.18; LRMS (ESI): Calcd. for C₁₅H₂₃ClO₄: ([M+NH₄]+) = 368.16, Found: 368.31; SFC OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, tᵣ (major) = 2.2 min tᵣ (minor) = 2.6 min, 97.2:2.5 er; [α]₀ = +35.2 (c = 0.03, DCM).

(2R,3S) tert-butyl -2-((R)-1-chloro-4-(trimethylsilyl)but-3-yn-1-yl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (2r): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester 1r (0.058 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2r (0.065 g, 0.15 mmol, 77% yield, 17:1 dr) as a white solid. The diastereomer ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.71 (minor diastereomer) and δ 4.32 (major diastereomer). Analytical data for 2r: mp 124.8-125.4 ºC; 1H NMR (600 MHz, CDCl₃) δ 7.40-7.36 (m, 3H), 7.27-7.26 (m, 2H), 4.28 (dd, J = 8.7, 2.2 Hz, 1H), 3.72 (dd, J = 10.7, 2.6 Hz, 1H), 3.04 (dd, J = 17.9, 8.6 Hz, 1H), 2.88 (dd, J = 17.7, 2.6 Hz, 1H), 2.70 (dd, J = 17.9, 2.2 Hz, 1H), 2.62 (dd, J = 17.7, 10.7 Hz, 1H), 1.55 (s, 9H), 0.09 (s, 9H); 13C NMR (151 MHz, CDCl₃): δ 174.5, 166.7, 136.7, 129.0, 128.6, 128.4, 118.5, 90.3, 84.5, 60.0, 46.9, 37.4, 36.3, 27.9; IR (thin film): 2980, 1799, 1734, 1248, 1151, 1122, 841, 699 cm⁻¹; TLC (10% EtOAc/hexane): Rᵣ = 0.17; LRMS (ESI): Calcd. for C₂₂H₃₅ClO₄Si: ([M+NH₄]+) = 438.19, Found: 438.33; SFC OD, 5% MeOH, flow rate = 3.0 mL/min, λ = 210 nm, tᵣ (major) = 2.1 min tᵣ (minor) = 2.4 min, 96.5:3.5 er; [α]₀ = +27.6 (c = 0.02, DCM).

(2R,3S) tert-butyl -2-((R)-2-(benzyloxy)-1 chloroethyl)-1-4-phenyltetrahydrofuran-2-carboxylate (2s): The title compound was prepared according to General Procedure B (Method 2) using α-keto ester 1s (0.065 g, 0.20 mmol), and (E)-cinnamaldehyde (0.04 mL, 0.40 mmol) affording 2s (0.030 g isomeric mix of products, 28% 1H NMR yield) as a colorless oil. The exact isomer ratio was not possible to determine. For product purity a second
chromatographic purification using an eluent gradient of 7.5-10% Et₂O/Hexanes was run after initial purification using EtOAc/Hexanes. Analytical data for 2s: \(^1\)H NMR (600 MHz, CDCl₃) \(\delta\) 7.35-7.26 (m, 10H), 4.43-4.38 (m, 2H), 4.22-4.21 (m, 1H), 3.68 (d, \(J = 10.9\) Hz, 1H), 3.33-3.31 (m, 2H), 3.09-2.98 (m, 1H), 2.74-2.71 (m, 1H), 2.02-1.86 (m, 2H), 1.80-1.69 (m, 2H), 1.56 (s, 9H), 1.43-1.39 (m, 2H); \(^1^3\)C NMR (151 MHz, CDCl₃): \(\delta\) 174.9, 167.5, 138.4, 128.7, 128.3, 128.3, 127.5, 127.5, 90.5, 84.3, 72.8, 69.2, 46.9, 36.3, 30.1, 27.9, 27.2, 26.9; IR (thin film): 2980, 1795, 1729, 1157, 1124, 697 cm\(^{-1}\); TLC (10% EtOAc/hexane): \(R_f\) = 0.12; LRMS (ESI): Calcd. for C\(_{26}\)H\(_{31}\)ClO\(_5\): ([M+NH\(_4^+\)]): 476.22, Found: 476.28; SFC OD, 10% MeOH, flow rate = 1.5 mL/min, \(\lambda = 210\) nm, \(t_R\) (major) = 8.1 min \(t_R\) (minor) = 9.0 min, 98.5:1.5 er; [\(\alpha\)]\(_D\) = +23.9 (c = 0.02, DCM).

**Procedure for the gram scale Asymmetric (3+2)-Annulation.**

![Chemical structure diagram]

To a flame dried 50 mL round bottom flask was added catalyst G, (0.19 mmol, 0.05 equiv) \(\beta\)-halo \(\alpha\)-keto ester 1a (3.5 mmol, 1.0 equiv), Et₂O (19 mL, 0.2 M) and (E)-3-(thiophen-2-yl)acrylaldehyde (7.0 mmol, 2.0 equiv). This solution stirred for 5 min followed by the addition of potassium carbonate (3.5 mmol, 1.0 equiv). This reaction was stirred (rate of stirring should be >800 rpm) for 14 h, filtered through a short plug of SiO₂ with 20% EtOAc/hexanes, and concentrated in vacuo. The resultant crude material was then stirred with 20% Et₂O/hexanes and filtered providing 2i (1.2 g, 84% yield, >30:1 dr, >99.5:0.5 er) as a white solid which was recrystallized from a 1:1 solution of DCM/MeOH by slow solvent evaporation providing crystals suitable for X-ray diffraction.

**Procedure for the hydrogenation of 2k.**

![Chemical structure diagram]

Step 2: A flame dried 20 mL scintillation vial equipped with a magnetic stir bar was charged with 10% Pd/C (3.0 mg). To the vial was added degassed ethanol (2 mL) and 2k (0.08 mmol, 1 equiv). The reaction vessel was purged with H\(_2\) (3 times), then put under 1 atm of H\(_2\) (balloon). The reaction mixture was stirred for 24 h, filtered through a plug of celite, then concentrated in vacuo providing 4k without need for further purification (0.35g, 0.08 mmol, 99% yield). Analytical data for 4k: \(^1\)H NMR (600 MHz,
CDCl₃) δ 7.35-7.22 (m, 8H), 7.17 (d, J = 7.5 Hz, 2H), 4.32-4.30 (m, 1H), 3.30-3.28 (m, 1H), 2.90-2.80 (m, 3H), 2.77-2.72 (m, 1H), 2.60-2.55 (m, 1H), 2.50 (dd, J = 17.6, 6.9 Hz, 1H), 2.39-2.34 (m, 1H), 1.83-1.76 (m, 1H), 1.48 (s, 9H); ¹³C NMR (151 MHz, CDCl₃): δ 173.9, 167.3, 139.9, 136.6, 129.3, 128.7, 128.5, 128.3, 127.2, 126.6, 89.4, 84.1, 77.2, 77.0, 76.8, 62.4, 41.2, 39.4, 34.2, 33.8, 30.1, 27.8; IR (thin film): 1790, 1752, 1128, 573 cm⁻¹; TLC (10% EtOAc/hexane): Rf = 0.08; LRMS (ESI): Calcd. for C₂₅H₂₉ClO₄: ([M+NH₄]⁺): 446.21, Found: 446.34; [α]₀ = -6.1 (c = 0.01, DCM).

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Crude $^1$H NMR of the Asymmetric (3+2)-Annulations for the determination of dr and product ratios
SFC Traces

2a

Signal 1: LVWD1 A, Wavelength=210 nm

| Peak # | RT [min] | Type | Width [mAU*sec] | Area [mAU] | Height [mAU] | Area % |
|--------|----------|------|----------------|------------|--------------|--------|
| 1      | 6.340    | MM   | 0.218          | 29002.276758 | 2213.49463 | 98.9262 |
| 2      | 10.162   | MM   | 0.273          | 314.81845  | 19.24926    | 1.0738 |

Totals: 29317.08594 2232.74390

**End of Report**
Signal 1: LWDD1 A, Wavelength=210 nm

| Peak | RT [min] | Type | Width [min] | Area [MAU×sec] | Height [MAU] | Area %     |
|------|----------|------|-------------|----------------|--------------|------------|
| 1    | 7.628    | MM   | 0.237       | 23148.82617    | 1629.14880   | 98.8524    |
| 2    | 11.992   | MM   | 0.377       | 2683.73148     | 113.99179    | 1.1476     |
| Totals: |          |      |             | 23417.55859    | 1641.04065   |            |

End of Report
**Signal 1: LW901 A, Wavelength=210 nm**

| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area % |
|------|----------|------|-------------|----------------|--------------|--------|
| 1    | 4.753    | MM   | 0.173       | 6095.88232     | 588.96820    | 97.2993|
| 2    | 7.095    | MM   | 0.242       | 169.20395      | 11.65232     | 2.7007 |

**Totals:**
6265.08643 600.62054

***End of Report***
### Signal 1: UWQDA, wavelength=210 nm

| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area [%] |
|------|----------|------|-------------|----------------|--------------|---------|
| 1    | 6.024    | MM   | 0.229       | 34789.94922    | 2532.68457   | 98.3889 |
| 2    | 9.714    | MM   | 0.281       | 3569.68201     | 33.84167     | 1.6111  |

**Totals:**
- **Area:** 35399.63281 mAU
- **Height:** 2566.52612 mAU

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***End of Report***
| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area [%] |
|------|---------|------|-------------|---------------|-------------|----------|
| 1    | 4.099   | MF   | 0.311       | 32221.24023   | 1727.62664  | 98.2496  |
| 2    | 6.669   | MM   | 0.477       | 574.05884     | 20.03774    | 1.7504   |

Totals: 32795.30078 1747.56728

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**End of Report**

S31
Signal 1: LVID1 A, Wavelength=210 nm

| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area % |
|------|----------|------|-------------|----------------|--------------|--------|
| 1    | 3.669    | MM   | 0.149       | 9685.09180     | 1083.82556   | 99.5308|
| 2    | 8.517    | MM   | 0.341       | 45.65810       | 2.22854      | 0.4692 |

Totals: 9730.75000 1086.05408

End of Report
**Signal 1: LVWD1 A, wavelength=210 nm**

| Peak | RT [min] | Type | Width [min] | Area [μAU•sec] | Height [μAU] | Area [%] |
|------|----------|------|-------------|----------------|--------------|---------|
| 1    | 4.301    | MM   | 0.183       | 27828.73633    | 2540.03784   | 96.5679 |
| 2    | 9.693    | MM   | 0.352       | 989.06431      | 46.81250     | 3.4321  |

**Totals:**

28817.80078 2586.89034

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**End of Report**

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S33
### Signal 1: LW01 A, Wavelength=210 nm

| Peak | RT (min) | Type | Width (min) | Area (MAU*sec) | Height (MAU) | Area % |
|------|----------|------|-------------|-----------------|--------------|--------|
| 1    | 8.852    | MM   | 0.284       | 4931.35205      | 289.37872    | 93.7842|
| 2    | 12.304   | MM   | 0.304       | 326.83853       | 17.91965     | 6.2158 |

**Totals:**

|                    | 5258.19043 | 307.29837 |

End of Report
Signal 1: LVWD1 A, Wavelength=210 nm

| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area % |
|------|---------|------|-------------|---------------|-------------|-------|
| 1    | 5.002   | FM   | 0.212       | 16981.43945   | 13812.14270 | 97.0465 |
| 2    | 6.933   | FM   | 0.302       | 516.81177     | 28.53217    | 2.9535 |
| Totals |        |      |             | 17498.25195   | 1366.67493  |       |

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End of Report

S36
| Peak | RT  | Type | Width | Area      | Height   | Area %  |
|------|-----|------|-------|-----------|----------|---------|
| 1    | 5.264 | MM   | 0.195 | 23660.74219 | 2023.58582 | 96.7996 |
| 2    | 6.682 | MM   | 0.225 | 782.28046  | 58.01243  | 3.2004  |

Totals: 24443.02344 2081.59814

*** End of Report ***
Signal 1: LVWD1 A, Wavelength=210 nm

| Peak # | RT [min] | Type | Width [min] | Area [mAU×sec] | Height [mAU] | Area % |
|--------|---------|------|-------------|----------------|--------------|--------|
| 1      | 2.162   | MM   | 0.095       | 11045.33398    | 1945.57678   | 97.4438 |
| 2      | 2.649   | MM   | 0.106       | 289.74448      | 45.42533     | 2.5562  |

Totals:  
11335.07813  1991.00208

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*** End of Report ***
| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area % |
|------|----------|------|-------------|----------------|--------------|--------|
| 1    | 2.107    | MF   | 0.096       | 3327.22412     | 580.41333    | 96.5180|
| 2    | 2.355    | FM   | 0.111       | 120.03503      | 18.05447     | 3.4820 |

Totals: 3447.25903  598.46777

*** End of Report ***
Signal 1: LVWD1 A, wavelength=210 nm

| Peak | RT [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area % |
|------|----------|------|-------------|----------------|--------------|--------|
| 1    | 8.098    | MM   | 0.299       | 12706.90820    | 709.11871    | 98.6061|
| 2    | 9.032    | MM   | 0.245       | 179.62059      | 12.23288     | 1.3939 |
| Totals: | | | | 12886.52832 | 721.35156 |

*** End of Report ***
$^1$H and $^{13}$C NMR Spectra
2c

\[ \text{Structure of } 2c \]

\[ \text{NMR Spectra of } 2c \]

S51
$^{13}$BuO$_2$C
Ph
Cl

$^2$m minor

$^{13}$BuO$_2$C
Ph
Cl

$^2$m minor
