Lewis Base Catalysis of Bromo- and Iodolactonization, and Cycloetherification

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SUPPORTING INFORMATION

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General Experimental

Dichloromethane (Fisher, HPLC grade) was dried by percolation through neutral alumina in a solvent dispensing system. ACS reagent grade ethyl acetate and hexanes used for chromatography and recrystallization were purchased from Fisher. Column chromatography was performed using Merck grade 9385, 60 Å silica gel. Visualization was accomplished by UV light and/or ceric ammonium molybdate solution and iodine vapor. Analytical and preparative thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. N-Bromosuccinimide was recrystallized from hot H₂O,¹ dried under vacuum at room temperature, stored at -20 °C, and protected from light. N-Iodosuccinimide was recrystallized from
dioxane/CCl₄, dried under vacuum at room temperature, ground in a mortar and pestle, stored at -20 °C and protected from light. Dioxane was distilled from Na freshly before use. Acetonitrile was distilled from CaH₂ freshly before use. Reagent grade CCl₄, TFA, AcOH, (CH₂)₄S, Me₂S, (Me₂N)₂C=O, (Me₂N)₂C=S, (PhSe)₂, (PhS)₂, (Me₂N)₃P=O, I₂ and Br₂ were purchased from Aldrich and used as received. n-Bu₃P=O was purchased from Aldrich and sublimed in vacuo before use. Ph₃P=S and n-Bu₃P were purchased from Strem and used as received. Me₂SO was purchased from Fischer and used as received. (Me₂N)₃P was distilled and stored in a sealed tube under argon.

¹H NMR and ¹³C NMR spectra were acquired in CDCl₃ at 500 MHz. Spectra were referenced to residual CHCl₃ (7.26 ppm ¹H; 77.00 ppm ¹³C). Assignments were obtained by reference to COSY and HMQC correlations. Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), hep (heptet), m (multiplet) and br (broad). Coupling constants, J, are reported in Hertz. Mass spectrometry was performed by the University of Illinois Mass Spectrometer Center. EI mass spectra were performed on a 70-VSE instrument. ESI mass spectra were performed on a Waters Q-Tof Ultima instrument. Data are reported in the form of (M/Z) versus intensity. Infrared spectra (IR) were recorded in KBr pellets or on NaCl plates. Peaks are reported in cm⁻¹ with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%); w (weak, 0-33%). In-situ FTIR reaction monitoring was performed on a Mettler-Toledo ReactIR 4000 instrument. Melting points (mp) were determined in sealed tubes and were corrected. Kugelrohr distillation temperatures reported are air bath temperatures (ABT).

**Literature Preparations**

(E)-6-Methyl-4-heptenoic acid 1c was prepared by Claisen rearrangement according to
the procedure of Orito and coworkers\(^2\). \((Z)-4\)-Phenyl-4-pentenoic acid \(1b\) was prepared by Wittig reaction according to the procedure of Borhan and co-workers\(^3\). \((E)-4\)-Phenyl-4-pentenoic acid \(1a\) was prepared by Claisen rearrangement according to the procedure of Gao and co-workers\(^4\). \((E)-7\)-Phenyl-hept-4-en-1-ol \(4b\) was prepared according to the procedure of Breidt\(^5\). \((Z)-7\)-Phenyl-hept-4-en-1-ol \(4c\) was prepared according to the procedure of Kang\(^6\). \(\text{Cy}_3\text{P}=\text{S}\), \(\text{Bu}_3\text{P}=\text{S}\), \((\text{Me}_2\text{N})_3\text{P}=\text{S}\), \(\text{Bu}_3\text{P}=\text{Se}\), \((\text{Me}_2\text{N})_3\text{P}=\text{Se}\) were prepared by reaction of their parent phosphines with elemental S or Se according to the procedures specified.

**Experimental Procedures**

**Lewis Base Catalyzed Bromolactonizations**

**General Procedure 1. Bromolactonization of \(1a\). Preparation of \(\text{rel-}(5\text{R},6\text{S})-5\)-Bromotetrahydro-6-phenyl-2H-pyran-2-one (2aa)\(^10\)**

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with \(N\)-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by a solution of \(1a\) (176.1 mg, 1.0 mmol, 1.0 equiv) in \(\text{CH}_2\text{Cl}_2\) (2.0 mL) via cannula. A solution of \(\text{Ph}_3\text{P}=\text{S}\) in \(\text{CH}_2\text{Cl}_2\) (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Saturated aq. \(\text{Na}_2\text{S}_2\text{O}_3\) solution (5 mL) was added, and the
resulting biphasic mixture was transferred to a 125-mL separatory funnel where it was diluted with H$_2$O (10 mL) and was extracted with CH$_2$Cl$_2$ (4 x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 2aa to 3aa was determined to be 90:1 by $^1$H NMR spectroscopy. The residue was purified by column chromatography (silica gel (18 g), 2 cm diam., CH$_2$Cl$_2$) to provide 207 mg (81%) of 2aa as a white solid.

Data for 2aa:

mp: 104 - 106 °C

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 7.45 – 7.35 (m, 1H, HC(Aryl)), 7.35 – 7.29 (m, 1H, HC(Aryl)), 5.57 (d, $J = 6.3$ Hz, 1H, HC(6)), 4.39 (td, $J = 6.5, 4.3$ Hz, 1H, HC(5)), 2.96 (dt, $J = 18.2, 7.8$ Hz, 1H, HC(3)), 2.72 (dt, $J = 18.2, 6.2$ Hz, 1H, HC(3')), 2.42 (dddd, $J = 14.8, 8.4, 6.6, 4.3$ Hz, 1H, HC(4)), 2.27 (ddd, $J = 14.3, 13.0, 6.7$ Hz, 1H, HC(4')).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

$\delta$ 169.0 (C(2)), 137.3 (C(7)), 129.1 (C(10)), 128.8 (C(8/9)), 126.4 (C(8/9)), 85.6 (C(6), 47.2 (C(5)), 28.4 (C(3/4)), 27.6 (C(3/4)).
General Procedure 2. *In-situ* IR Monitoring of the Bromolactonization of 1a in the Presence of (Me₂N)₂C=O (Table 1, entry 2)

An oven-dried, 3-necked React-IR cell was fitted with a magnetic stir bar, a septum and a stopper. The cell was fitted to the React-IR probe (DiComp), and purged with argon through an oil bubbler. Dichloromethane (0.8 mL) was added via syringe, and a background spectrum was acquired (2 cm⁻¹ resolution, 700 – 1900 cm⁻¹, 256 scans). The apparatus was wrapped in Al foil, and N-bromosuccinimide (43 mg, 0.24 mmol, 1.2 equiv.) was added under positive argon flow. Dichloromethane (0.2 mL) was added. Data acquisition was begun (2 cm⁻¹ resolution, 32 scans, 35 seconds/spectrum). A solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (12.6 mg) in CH₂Cl₂ (0.4 mL) was added via short cannula. After a delay to verify the stability of data acquisition and the homogeneity of the reaction mixture, a solution of (Me₂N)₂C=O in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv) was added rapidly via syringe. The reaction mixture was allowed to stir for 3 h while the disappearance of 1a was monitored by its absorption at 967 cm⁻¹. The half-life of the reaction was observed to be > 180 min. The reaction mixture was quenched with saturated aq. Na₂S₂O₃ solution (1 mL), diluted with CH₂Cl₂ (4 mL) and allowed to stir for 20 min. An aliquot (ca. 4 mL) was taken from the organic phase, concentrated in vacuo, and analyzed by ¹H NMR spectroscopy (4 scans, δ1= 40 sec). A yield of 36% was calculated by comparing the integrated area of the signal of 1,2,4,5-C₆H₂Cl₄ (δ 7.5 (s,
2H)) with the combined areas of the signals for H-6 of 2aa (δ 5.56 (d, J = 6.4 Hz, 1H)) and 3aa (δ 5.01(d, J = 7.0 Hz, 1H)). The ratio of integrals for H-6 of 2aa and 3aa was 23:1.

**Bromolactonization of 1a in the Absence of a Catalyst (Table 1, entry 1)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL) and a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (13.1 mg) in CH₂Cl₂ (0.5 mL). The half-life of the reaction was observed to be > 180 min. After stirring for 3 h and quenching, 13% yield and a 25:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of n-Bu₃P=O (Table 1, entry 3)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.1 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (15.5 mg) in CH₂Cl₂ (0.4 mL) and a solution of n-Bu₃P=O in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life of the reaction was observed to be > 180 min. After stirring for 3 h and quenching, 47% yield and a 51:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (Me₂N)₃P=O (Table 1, entry 4)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (11.5 mg) in CH₂Cl₂ (0.4 mL), and a solution of (Me₂N)₃P=O in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life of the reaction
was observed to be > 180 min. After stirring for 3 h and quenching, 15% yield and a 50:1 ratio of 2aa:3aa were observed by $^1$H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of Me$_2$SO (Table 1, entry 5)**

Following General Procedure 2, a React-IR cell was charged with CH$_2$Cl$_2$ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH$_2$Cl$_2$ (0.2 mL), a solution of 1a (34.9 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C$_6$H$_2$Cl$_4$ (12.1 mg) in CH$_2$Cl$_2$ (0.4 mL) and a solution of Me$_2$SO in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 25 min. After stirring for 1 h and quenching, 93% yield and a 23:1 ratio of 2aa:3aa were observed by $^1$H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (Me$_2$N)$_2$C=S (Table 1, entry 6)**

Following General Procedure 2, a React-IR cell was charged with CH$_2$Cl$_2$ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH$_2$Cl$_2$ (0.2 mL), a solution of 1a (35.6 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C$_6$H$_2$Cl$_4$ (11.6 mg) in CH$_2$Cl$_2$ (0.4 mL) and a solution of (Me$_2$N)$_2$C=S in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 71% yield and a 7.3:1 ratio of 2aa:3aa were observed by $^1$H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of Ph$_3$P=S (Table 1, entry 7)**

Following General Procedure 2, a React-IR cell was charged with CH$_2$Cl$_2$ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH$_2$Cl$_2$ (0.2 mL), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C$_6$H$_2$Cl$_4$ (15.6 mg) in CH$_2$Cl$_2$ (0.4 mL) and a solution of
Ph₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 82% yield and a 91:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of n-Bu₃P=S (Table 1, entry 8)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (10.5 mg) in CH₂Cl₂ (0.4 mL) and a solution of n-Bu₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 89% yield and a 75:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of Cy₃P=S (Table 1, entry 9)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (34.7 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (12.9 mg) in CH₂Cl₂ (0.4 mL) and a solution of Cy₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 78% yield and a 25:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (Me₂N)₃P=S (Table 1, entry 10)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.4
mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (10.1 mg) in CH₂Cl₂ (0.4 mL) and a solution of (Me₂N)₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 87% yield and a 3.4:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy. All material was combined and transferred to a 60-mL separatory funnel, where it was extracted with CH₂Cl₂ (3 x 3 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel (4.5 g), 1 cm diam., hexane/EtOAc 4:1) to provide 22.6 mg (44%) of 2aa as a white solid, and 21.3 mg (42 %) of a 1.3:1 mixture of 2aa and 3aa as a white solid.

**Data for 3aa:**

¹H NMR:  (500 MHz, CDCl₃)

δ 5.01 (d, J = 6.9 Hz, 1H, HC(6)), 4.97 – 4.86 (m, 1H, HC(5)), 2.57 – 2.46 (m, 3H, H₂C(3, 4)), 2.32-2.20 (m, 1H, H₂C(3, 4))

¹³C NMR:  (125 MHz, CDCl₃)

δ 175.9 (C(2)), 137.1 (C(7)), 128.8 (C(8/9/10)), 128.2 (C(8/9/10)), 126.4(C(8/9/10)), 81.6 (C(5)), 55.4 (C(6)), 28.5 (C(3/4)), 26.4 C(3/4)).

IR:  (neat)

1779 (s, 2aa), 1747 (s, 3aa).

**Bromolactonization of 1a in the Presence of (CH₂)₄S (Table 1, entry 11)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.2 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (11.8 mg) in CH₂Cl₂ (0.4 mL) and a solution of
(CH₂)₄S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 89% yield and a 27:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of Me₂S (Table 1, entry 12)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.1 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (11.3 mg) in CH₂Cl₂ (0.4 mL) and a solution of Me₂S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 6 min. After stirring for 20 min and quenching, 94% yield and a 19:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (PhS)₂ (Table 1, entry 13)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (12.0 mg) in CH₂Cl₂ (0.4 mL) and a solution of (PhS)₂ in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 8% yield was observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of n-Bu₃P=Se (Table 1, entry 14)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (34.9 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (10.9 mg) in CH₂Cl₂ (0.4 mL) and a solution of n-
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$\text{Bu}_3\text{P}=\text{Se}$ in $\text{CH}_2\text{Cl}_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 30 sec. After stirring for 8 min and quenching, 78% yield and an 85:1 ratio of $2\text{aa}:3\text{aa}$ were observed by $^1\text{H}$ NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (Me$_2$N)$_3\text{P}=\text{Se}$ (Table 1, entry 15)**

Following General Procedure 2, a React-IR cell was charged with $\text{CH}_2\text{Cl}_2$ (0.8 mL) and $N$-bromosuccinimide (43 mg, 0.24 equiv), followed by $\text{CH}_2\text{Cl}_2$ (0.2 mL), a solution of 1a (35.0 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-$\text{C}_6\text{H}_2\text{Cl}_4$ (11.5 mg) in $\text{CH}_2\text{Cl}_2$ (0.4 mL) and a solution of (Me$_2$N)$_3\text{P}=\text{Se}$ in $\text{CH}_2\text{Cl}_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 88% yield and an 8.1:1 ratio of $2\text{aa}:3\text{aa}$ were observed by $^1\text{H}$ NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (PhSe)$_2$ (Table 1, entry 16)**

Following General Procedure 2, a React-IR cell was charged with $\text{CH}_2\text{Cl}_2$ (0.8 mL) and $N$-bromosuccinimide (43 mg, 0.24 equiv), followed by $\text{CH}_2\text{Cl}_2$ (0.2 mL), a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-$\text{C}_6\text{H}_2\text{Cl}_4$ (11.7 mg) in $\text{CH}_2\text{Cl}_2$ (0.4 mL) and a solution of (PhSe)$_2$ in $\text{CH}_2\text{Cl}_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be between 35 sec and 70 sec. After stirring for 8 min and quenching, 84% yield and a 94:1 ratio of $2\text{aa}:3\text{aa}$ were observed by $^1\text{H}$ NMR spectroscopy.

**Bromolactonization of 1a in the Presence of n-Bu$_3$P (Table 1, entry 17)**

Following General Procedure 2, a React-IR cell was charged with $\text{CH}_2\text{Cl}_2$ (0.8 mL) and $N$-bromosuccinimide (43 mg, 0.24 equiv), followed by $\text{CH}_2\text{Cl}_2$ (0.2 mL), a solution of 1a (35.4
mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (12.0 mg) in CH₂Cl₂ (0.4 mL) and a solution of n-Bu₃P in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 5 min and quenching, 75% yield and a 38:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of (Me₂N)₃P (Table 1, entry 18)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (11.8 mg) in CH₂Cl₂ (0.4 mL) and a solution of (Me₂N)₃P in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 86% yield and a 6.7:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.

**Bromolactonization of 1a in the Presence of Br₂ (Table 1, entry 19)**

Following General Procedure 2, a React-IR cell was charged with CH₂Cl₂ (0.8 mL) and N-bromosuccinimide (43 mg, 0.24 equiv), followed by CH₂Cl₂ (0.2 mL), a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and 1,2,4,5-C₆H₂Cl₄ (11.3 mg) in CH₂Cl₂ (0.4 mL) and a solution of Br₂ in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be < 35 sec. After stirring for 8 min and quenching, 64% yield and a 400:1 ratio of 2aa:3aa were observed by ¹H NMR spectroscopy.
Bromolactonization of 1b. Preparation of *rel*-**(5R)-Dihydro-5-[(R)-bromophenylmethyl]-2(3H)-furanone** (3ba)

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with *N*-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by a solution of 1b (176.1 mg, 1.0 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.0 mL) via cannula. A solution of (Me$_2$N)$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Saturated aq. Na$_2$S$_2$O$_3$ solution (5 mL) was added, and the resulting biphasic mixture was transferred to a 125-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 2ba to 3ba was determined to be 1:40 by $^1$H NMR spectroscopy. The residue was purified by column chromatography (silica gel (19 g), 2 cm diam., CH$_2$Cl$_2$), to provide 211 mg (83%) of 3ba as a white solid, which was recrystallized from hot EtOAc/hexanes (ca. 0.3 mL/ 5 mL) to provide 206 mg (81%) of 3ba as colorless plates.

**Data for 3ba:**

mp: 126 – 129 °C

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 7.62 – 7.41 (m, 2H, HC(Aryl)), 7.41 – 7.24 (m, 3H, HC(Aryl)), 4.99 (d, $J = 5.5$
Hz, 1H, HC(6)), 4.91 (td, J = 7.0, 5.6 Hz, 1H, HC(5)), 2.55 – 2.33 (m, 2H, H₂C(3)),
2.31 – 2.17 (m, 1H, HC(4)), 2.05 (ddd, J = 13.4, 10.0, 8.4, 6.8 Hz, 1H, HC(4)).

^{13}C NMR: (125 MHz, CDCl₃)
δ 175.9 (C(2)), 136.8 (C(7)), 129.1 (C(10)), 128.8 (C(8/9)), 128.4 (C(8/9)), 81.9
(C(5)), 55.1 (C(6)), 28.3 (C(3)), 25.6 (C(4)).

IR: (KBr pellet)
3064 (w), 2936 (w), 1777 (s), 1458 (w), 1419 (w), 1335 (w), 1175 (s), 1146 (m),
1052 (m), 1030 (m), 918 (m), 870 (w), 783 (w), 706 (s), 664 (m), 597 (w).

MS: (EI, 70 eV)
85 (100), 91 (25), 175 (47), 254 (1, M^{79}Br⁺), 256 (1, M^{81}Br⁺).

TLC: Rf 0.11 (hexanes/EtOAc, 4:1) [UV]

Analysis: C₁₁H₁₁O₂Br (255.1)
Calcd: C, 51.79; H, 4.35;
Found: C, 51.52; H, 4.24;

Bromolactonization of 1b in the Presence of Ph₃P=S.

A 5-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was
charged with N-bromosuccinimide (21 mg, 0.12 mmol, 1.2 equiv). The flask was wrapped in Al-
foil and then was evacuated and filled with argon. Dichloromethane (0.5 mL) was added via
syringe. Neat 1b (17.2 mg, 0.1 mmol, 1.0 equiv) was added via syringe, followed by CH₂Cl₂ (0.2 mL). A solution of Ph₃P=S in CH₂Cl₂ (50 μL, 0.1 M, 0.05 equiv, 0.005 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min. Sat. aq. Na₂S₂O₃ solution (1 mL) was added, and the resulting biphasic mixture was transferred to a 60-mL separatory funnel where it was diluted with brine (4 mL) and H₂O (1 mL) and was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo (23 °C, 10 mmHg). A 1.4:1 mixture of 3ba and 2ba was observed by ¹H NMR spectroscopy. The residue was purified by column chromatography (silica gel (4.5 g), 1 cm diam., gradient from hexane/CH₂Cl₂ 1:1 to 0:1), to provide 9.8 mg (39%) of a 7.7:1 mixture of 3ba and 2ba, and 5.9 mg (24%) of a 0.02:1 mixture of 3ba and 2ba.

Data for 2ba:

¹H NMR: (500 MHz, CDCl₃)

δ 7.45 – 7.32 (m, 5H, HC(Aryl)), 5.49 (d, J = 1.5 Hz, 1H, HC(6)), 4.58 (m, 1H, HC(5)), 3.05 (ddd, J = 18.7, 10.9, 8.0 Hz, 1H, HC(3)), 2.79 (ddd, J = 18.6, 7.3, 1.9 Hz, 1H, HC(3’)), 2.63 (dddd, J = 14.4, 10.8, 7.3, 3.3 Hz, 1H, HC(4)), 2.49 (dddd, J = 14.5, 7.9, 3.3, 2.2 Hz, 1H, HC(4’)).
Bromolactonization of 1c. Preparation of rel-(5R)-5-[(1'S)-1'-Bromo-2’-methylpropyl]dihydro-2(3H)-furanone (3ca)

A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with N-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by 1c (141.8 mg, 1.0 mmol, 1.0 equiv) via syringe and CH$_2$Cl$_2$ (2.0 mL) via syringe. A solution of (Me$_2$N)$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Sat. aq. Na$_2$S$_2$O$_3$ solution (5 mL) was added, and the resulting biphasic mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ (25 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo (23 °C, 10 mmHg). The residue was purified by column chromatography (silica gel (37 g), 3 cm diam., hexane/EtOAc, 80:20), followed by bulb-to-bulb distillation (100 – 110 °C, 0.46 mmHg) to provide 193.1 mg (88%) of a 6:1 mixture of 3ca and 2ca as a colorless oil.

Data for 3ca:

bp: 100 – 110 °C (0.46 mmHg, ABT)

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 4.66 – 4.55 (m, 1H, HC(5)), 3.94 (dd, $J$ = 9.0, 3.3 Hz, 1H, HC(6)), 2.59 – 2.46 (m,
3H, HC(4, 3, 3’), 2.16 (dtt, J = 13.3, 6.6, 3.4 Hz, 1H, HC(7)), 2.13 – 2.04 (m, 1H, HC(4’)), 1.02 (d, J = 6.7 Hz, 3H, H$_3$C(8)), 0.98 (d, J = 6.5 Hz, 3H, H$_3$C(9)).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

$\delta$ 176.3 (C(2)), 79.5 (C(5)), 65.8 (C(6)), 30.0 (C(7)), 28.4 (C(3)), 27.5 (C(4)), 21.3 (C(8)), 16.8 (C(9)).

IR: (neat)

2968 (s), 2879 (m), 1790 (s), 1464 (m), 1421 (m), 1370 (m), 1334 (m), 1174 (s), 1116 (m), 1023 (s), 991 (m), 912 (m), 871 (m), 823 (m), 803 (m), 705 (w), 666 (m), 529 (w).

MS: (EI, 70 eV)

55 (12), 85 (100), 99 (6), 141 (6), 219 (M$^{79}$Br – H$^-$, 2), 221 (M$^{81}$Br – H$^-$, 2).

TLC: $R_f$ 0.29 (hexanes/EtOAc, 4:1) [UV/I$_2$/CAM]

Analysis: C$_8$H$_{13}$O$_2$ Br (221.1)

Calcd: C, 43.46; H, 5.93;
Found: C, 43.68; H, 5.90;

Data for 2ca:

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 4.31 (dd, J = 8.2, 3.7 Hz, 1H, HC(6)), 4.19 (td, J = 8.0, 5.0 Hz, 1H, HC(5)), 2.79 (tt, J = 15.7, 7.8 Hz, 1H, HC(3)), 2.60-2.52 (m, 1H, HC(3’)), 2.50 – 2.40 (m, 1H, HC(4)), 2.33 (dt, J = 14.3, 6.7 Hz, 1H, HC(4’)), 2.29-2.24 (m, 1H, HC(7)) 1.10 (d, J = 7.0 Hz, 3H, H$_3$C(8)), 1.00 (d, J = 6.8 Hz, 3H, H$_3$C(9)).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

$\delta$ 87.6 (C(6)), 44.0 (C(5)), 30.3, 29.5, 28.94, 19.3 (C(8)), 15.1 (C(9)).
**IR**: (KBr pellet)

1748 (s).

**Lewis Base Catalyzed Bromocycloetherifications**


![](image)

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with N-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by a solution of 4a (162.0 mg, 1.0 mmol, 1.0 equiv) and AcOH (57 µL, 1.0 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) via cannula. A solution of Ph₃P=S in CH₂Cl₂ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Saturated aq. Na₂S₂O₃ solution (5 mL) and sat. aq. NaHCO₃ solution (5 mL) were added, and the resulting biphasic mixture was transferred to a 125-mL separatory funnel where it was diluted with H₂O (20 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 5aa to 6aa was determined to be 11:1 by ¹H NMR spectroscopy. The residue was purified by column chromatography (silica gel (35 g), 3 cm diam., hexane/EtOAc, 95:5) to provide 166.5 mg (69%)
of 5aa as colorless needles.

**Data for 5aa:**

- **mp:** 41 – 42 °C
- **$^1$H NMR:** (500 MHz, CDCl$_3$)
  \[
  \delta 7.42 – 7.29 (m, 5H, HC(Aryl)), 4.32 (d, J = 10.0 Hz, 1H, HC(2)), 4.14 (ddt, J = 11.4, 4.5, 1.6 Hz, 1H, HC(6)), 4.06 (ddd, J = 11.7, 10.1, 4.4 Hz, 1H, HC(3)), 3.65 (td, J = 12.0, 2.2 Hz, 1H, HC(6’)), 2.65 – 2.54 (m, 1H, HC(4/5)), 2.13 (tdd, J = 13.0, 11.6, 4.2 Hz, 1H, HC(4’)), 1.95 (dddd, J = 13.8, 13.1, 12.3, 4.7, 3.8 Hz, 1H, HC(5’)), 1.83 – 1.70 (m, 1H, HC(4/5))

**Bromocycloetherification of 4b. Preparation of rel-(2R)-Tetrahydro-2-[(1’S)-1’-bromo-3-phenylpropyl]furan (6ba)**

A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with $N$-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by 4c (189.7 mg, 1.0 mmol, 1.0 equiv), AcOH (57 µL, 1.0 mmol, 1.0 equiv), and CH$_2$Cl$_2$ (2.0 mL). A solution of Ph$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Sat. aq. Na$_2$S$_2$O$_3$ solution (5 mL) and sat. aq. NaHCO$_3$ solution (5 mL) were added. The resulting biphasic mixture was transferred to a 250-
mL separatory funnel where it was diluted with H₂O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ solution (25 mL) and brine (25 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 6ba to 5ba was determined to be 12:1 by ¹H NMR spectroscopy. The residue was purified by column chromatography (silica gel (36 g), 3 cm diam., hexane/EtOAc, 95:5), to provide a light straw-colored oil, which was further purified by bulb-to-bulb distillation (55 - 65 °C, 3.4 x 10⁻⁵ mmHg) to provide 223.1 mg (83%) of 6ba as a colorless oil.

Data for 6ba:

bp: 55 – 65 °C (ABT, 3.4 x 10⁻⁵ mmHg)

¹H NMR: (500 MHz, CDCl₃)

δ 7.33 – 7.27 (m, 2H, HC(argon)), 7.25 – 7.18 (m, 3H, HC(argon)), 3.99 (q, J = 6.7 Hz, 1H, HC(2)), 3.93 (ddd, J = 9.9, 7.0, 2.8 Hz, 1H, HC(6)), 3.89 (dt, J = 14.3, 6.8 Hz, 1H, H₂C(5/5’)), 3.85 – 3.79 (m, 1H, H₂C(5/5’)), 2.98 (ddd, J = 13.9, 9.3, 4.7 Hz, 1H, H₂C(8/8’)), 2.75 (ddd, J = 13.8, 9.1, 7.4 Hz, 1H, H₂C(8/8’)), 2.37 – 2.25 (m, 1H, H₂C(7/7’)), 2.16 – 2.07 (m, 1H, H₂C(3/3’)), 2.07 – 1.98 (m, 1H, H₂C(7/7’)), 1.98 – 1.75 (m, 3H, H₂C(3/3’, 4, 4’)).

¹³C NMR: (125 MHz, CDCl₃)

δ 140.9 (C(9)), 128.5 (C(10/11)), 128.4 (C(10/11)), 126.0 (C(12)), 81.8 (C(2)), 68.9 (C(5)), 59.3 (C(6)), 36.9 (C(7)), 33.4 (C(8)), 30.2 (C(3)), 25.9 (C(4)).

IR: (neat)

3062 (w), 3027 (m), 2950 (s), 2865 (s), 1603 (m), 1497 (m), 1454 (s), 1357 (w), 1283 (w), 1192 (m), 1061 (s), 926 (m), 750 (s), 700 (s), 626 (w).
**MS:** (EI, 70 eV)

55 (18), 65 (13), 71 (13), 87 (20), 91 (100), 92 (15), 97 (31), 104 (36), 105 (21), 115 (18), 117 (32), 129 (13), 141 (13), 143 (23), 145 (12), 162 (11), 164 (10), 169 (45), 187 (72), 188 (14), 205 (13), 267 (37, M$^{79}$Br - H), 269 (34, M$^{81}$Br - H).

**TLC:** R$_f$ 0.22 (hexanes/EtOAc, 19:1) [UV]

**Analysis:** C$_{13}$H$_{17}$O Br (269.2)

Calcd: C, 58.01; H, 6.37;

Found: C, 58.10; H, 6.28;

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**Bromocycloetherification of 4c. Preparation of rel-(2R)-Tetrahydro-2-[(1'R)-1’-bromo-3-phenylpropyl]furan (6ca)**

A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar, was charged with N-bromosuccinimide (213 mg, 1.2 mmol, 1.2 equiv). The flask was wrapped in Al-foil and then was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe, followed by 4c (189.7 mg, 1.0 mmol, 1.0 equiv), AcOH (57 µL, 1.0 mmol, 1.0 equiv), and CH$_2$Cl$_2$ (2.0 mL). A solution of Ph$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe, and the resulting solution was stirred for at room temperature for 5 min after which a yellow color was observed. Saturated aq. Na$_2$S$_2$O$_3$ solution (5 mL) and sat. aq. NaHCO$_3$ solution (5 mL) were added, and the resulting biphasic mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with EtOAc
(3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ solution (25 mL) and brine (25 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 6ca to 5ca was determined to be >19:1 by ¹H NMR spectroscopy. The residue was purified by column chromatography (silica gel (35 g), 3 cm diam., hexane/EtOAc, 95:5), to provide 205.5 mg of a light straw-colored oil, which was further purified by bulb-to-bulb distillation (60 - 75 °C, 3.4 x 10⁻⁵ mmHg) to provide 201.5 mg (75%) of 6ca as a colorless oil.

Data for 6ca:

bp: 60 – 75 °C (ABT, 3.4 x 10⁻⁵ mmHg)

¹H NMR: (500 MHz, CDCl₃)

δ 7.34 – 7.27 (m, 2H, HC(argon)), 7.25 – 7.16 (m, 3H, HC(argon)), 4.05 – 3.98 (m, 1H, HC(2)), 3.98 – 3.90 (m, 2H, HC(6, 5/5’)), 3.82 (td, J = 7.7, 5.7 Hz, 1H, H₂C(5/5’)), 2.98 (ddd, J = 13.7, 8.2, 5.5 Hz, 1H, HC(8/8’)), 2.77 (dt, J = 13.8, 8.2 Hz, 1H, HC(8/8’)), 2.21–2.11 (m, 2H, HC(7,7’)), 2.06 – 1.94 (m, 3H, HC(3, 4, 4’)), 1.82 – 1.72 (m, 1H, HC(3’)).

¹³C NMR: (125 MHz, CDCl₃)

δ 140.8 (C(9)), 128.5 (C(10/11)), 128.4 (C(10/11)), 126.1 (C(12)), 81.7 (C(2)), 68.9 (C(5)), 58.9 (C(6)), 36.5 (C(7)), 33.7 (C(8)), 29.5 (C(3)), 26.1 (C(4)).

IR: (neat)

3062 (m), 3026 (m), 2951 (s), 2865 (s), 1603 (m), 1496 (s), 1454 (s), 1358 (m), 1289 (w), 1239 (m), 1058 (s), 1030 (m), 925 (m), 750 (s), 700 (s), 621 (w).

MS: (EI, 70 eV)

55 (16), 65 (18), 74 (84), 77 (10), 87 (14), 91 (100), 92 (14), 97 (38), 104 (29), 105
Lewis Base Catalyzed Iodolactonizations

General Procedure 3. Iodolactonization of 1a. Preparation of \textit{rel-(5\textit{R},6\textit{S})-5-iodotetrahydro-6-phenyl-2H-pyran-2-one (2ab)}\textsuperscript{4}

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with \textit{N}-iodosuccinimide (270 mg, 1.2 mmol, 1.2 equiv). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to -45 °C (\textit{CO}_2/MeCN bath, internal temp). A solution of 1a (176.0 mg, 1.0 mmol, 1.0 equiv) and TFA (3.8 µL, 0.05 mmol, 0.05 equiv) in \textit{CH}_2\textit{Cl}_2 (2.0 mL) was added via cannula. Next, a solution of \textit{n-Bu}_3\textit{P=S} in \textit{CH}_2\textit{Cl}_2 (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at -45 °C for 2 h, and then a solution of butyl vinyl ether in EtOH (2.5 mL, 1.2 M, 3.0 equiv) was added. After 5 min, sat. aq. \textit{Na}_2\textit{S}_2\textit{O}_3 solution (5 mL) was added and the resulting biphasic mixture was allowed to warm to room temperature. Saturated aq. NaHCO\textsubscript{3} solution (5 mL) was added and the
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reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (20 mL) and was extracted with EtOAc (3 x 25 mL). The ratio of 2ab to 3ab was determined to be 32:1 by $^1$H NMR spectroscopy. The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). The residue was purified by column chromatography (silica gel (35 g), 3 cm diam., hexane/EtOAc, 80:20) to provide 183.4 mg (61%) of 2ab as a white solid.

Data for 2ab:

mp: 68 – 76 °C (dec.)

$^1$H NMR: (500 MHz, CDCl$_3$)

δ 7.44 – 7.36 (m, 3H, HC(Aryl)), 7.36 – 7.29 (m, 2H, HC(Aryl), 5.56 (d, $J = 7.8$ Hz, 1H, HC(6)), 4.42 (td, $J = 8.0$, 4.6 Hz, 1H, HC(5)), 2.86 (dt, $J = 18.1$, 6.9 Hz, 1H, HC(3)), 2.72 (dt, $J = 18.2$, 6.9 Hz, 1H, HC(3’)), 2.51 – 2.33 (m, 2H, H$_2$C(4)).

General Procedure 3. In-situ IR Monitoring of the Iodolactonization of 1a in the Presence of (Me$_2$N)$_2$C=O.

An oven-dried, 3-necked React-IR cell was fitted with a magnetic stir bar, a septum, a thermometer adapter and a thermocouple. The cell was fitted to the React-IR probe (DiComp), and was wrapped in Al foil. N-iodosuccinimide (54 mg, 0.24 mmol, 1.2 equiv) was added and the cell was purged with argon through an oil bubbler. Dichloromethane (1.0 mL) was added via
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syringe, the cell was cooled to -45 °C and a background spectrum was acquired (2 cm⁻¹ resolution, 700 – 1900 cm⁻¹, 256 scans). Data acquisition was begun (2 cm⁻¹ resolution, 32 scans, 35 seconds/spectrum). A solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (12.6 mg) in CH₂Cl₂ (0.4 mL) was added via a short cannula. After a delay to verify the stability of data acquisition and the efficient stirring of the reaction mixture, a solution of (Me₂N)₂C=O in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv) was added rapidly via syringe. The reaction mixture was allowed to stir for 3 h while the disappearance of 1a was monitored by its absorption at 967 cm⁻¹. The half-life was observed to be >180 min. The reaction mixture was quenched with a solution of butyl vinyl ether in EtOH (0.5 mL, 1.2 M, 3.0 equiv) and was allowed to stir at -45 °C for 15 min. Saturated aq. Na₂S₂O₅ solution (1 mL) was added and the resulting biphasic mixture was allowed to warm to room temperature, then was diluted with CH₂Cl₂ (4 mL) and was allowed to stir for 20 min. An aliquot (ca. 4 mL) was taken from the organic phase, concentrated in vacuo, and analyzed by ¹H NMR spectroscopy (4 scans, δ₁= 40 sec). A yield of 10% was calculated by comparing the integrated area of the signal of C₆Me₆ (δ 2.24 (s, 18H)) with the combined areas of the signals for H-6 of 2ab (δ 5.56 (d, J = 7.9 Hz, 1H)) and 3ab (δ 5.13 (d, J = 7.9 Hz, 1H))⁴. The ratio of integrals for H-6 of 2ab and 3ab was 20:1.

**Iodolactonization of 1a in the Absence of a Catalyst (Table 2, entry 1)**

Following General Procedure 3, a React-IR cell was charged with CH₂Cl₂ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), and a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (11.1 mg) in CH₂Cl₂ (0.5 mL). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 4% yield and a 9.5:1 ratio of 2ab:3ab were observed by ¹H NMR spectroscopy.
Iodolactonization of 1a in the Presence of \( n\text{-Bu}_3\text{P}=\text{O} \) (Table 2, entry 3)

Following General Procedure 3, a React-IR cell was charged with \( \text{CH}_2\text{Cl}_2 \) (1.0 mL), \( \text{N-iodosuccinimide} \) (54 mg, 0.24 equiv), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and \( \text{C}_6\text{Me}_6 \) (11.6 mg) in \( \text{CH}_2\text{Cl}_2 \) (0.4 mL), and a solution of \( n\text{-Bu}_3\text{P}=\text{O} \) in \( \text{CH}_2\text{Cl}_2 \) (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be \( >180 \text{ min} \). After stirring for 3 h and quenching, 14% yield and a 16:1 ratio of \( 2\text{ab}:3\text{ab} \) were observed by \( ^1\text{H} \) NMR spectroscopy.

Iodolactonization of 1a in the Presence of (\( \text{Me}_2\text{N} \))\(_3\text{P}=\text{O} \) (Table 2, entry 4)

Following General Procedure 3, a React-IR cell was charged with \( \text{CH}_2\text{Cl}_2 \) (1.0 mL), \( \text{N-iodosuccinimide} \) (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and \( \text{C}_6\text{Me}_6 \) (10.4 mg) in \( \text{CH}_2\text{Cl}_2 \) (0.4 mL), and a solution of (\( \text{Me}_2\text{N} \))\(_3\text{P}=\text{O} \) in \( \text{CH}_2\text{Cl}_2 \) (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be \( >180 \text{ min} \). After stirring for 3 h and quenching, 33% yield and a 20:1 ratio of \( 2\text{ab}:3\text{ab} \) were observed by \( ^1\text{H} \) NMR spectroscopy.

Iodolactonization of 1a in the Presence of \( \text{Me}_2\text{SO} \) (Table 2, entry 5)

Following General Procedure 3, a React-IR cell was charged with \( \text{CH}_2\text{Cl}_2 \) (1.0 mL), \( \text{N-iodosuccinimide} \) (54 mg, 0.24 equiv), a solution of 1a (35.2 mg, 0.2 mmol, 1.0 equiv) and \( \text{C}_6\text{Me}_6 \) (10.3 mg) in \( \text{CH}_2\text{Cl}_2 \) (0.4 mL), and a solution of \( \text{Me}_2\text{SO} \) in \( \text{CH}_2\text{Cl}_2 \) (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be \( >180 \text{ min} \). After stirring for 3 h and quenching, 4% yield was observed by \( ^1\text{H} \) NMR spectroscopy.

Iodolactonization of 1a in the Presence of (\( \text{Me}_2\text{N} \))\(_2\text{C}=\text{S} \) (Table 2, entry 6)
Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (10.6 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of (Me$_2$N)$_2$C=S in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 4 min. After stirring for 1 h and quenching, 91% yield and a 4.7:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of Ph$_3$P=S (Table 2, entry 7)**

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.2 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (10.2 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of Ph$_3$P=S in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 35 min. After stirring for 1 h and quenching, 92% yield and a 5.5:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of n-Bu$_3$P=S (Table 2, entry 8)**

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (11.8 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of n-Bu$_3$P=S in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 7 min. After stirring for 1 h and quenching, 72% yield and a 6.1:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of Cy$_3$P=S (Table 2, entry 9)**

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-
iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (10.5 mg) in CH₂Cl₂ (0.4 mL), and a solution of Cy₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 8 min. After stirring for 1 h and quenching, 93% yield and a 1.7:1 ratio of 2ab:3ab were observed by ¹H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of ( Me₂N)₃P=S (Table 2, entry 10)**

Following General Procedure 3, a React-IR cell was charged with CH₂Cl₂ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (10.1 mg) in CH₂Cl₂ (0.4 mL), and a solution of (Me₂N)₃P=S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 4 min. After stirring for 1 h and quenching, 97% yield and a 2.5:1 ratio of 2ab:3ab were observed by ¹H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of (CH₂)₄S (Table 2, entry 11)**

Following General Procedure 3, a React-IR cell was charged with CH₂Cl₂ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.1 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (13.1 mg) in CH₂Cl₂ (0.4 mL), and a solution of (CH₂)₄S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 10 min. After stirring for 1 h and quenching, 97% yield and a 5.8:1 ratio of 2ab:3ab were observed by ¹H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of Me₂S (Table 2, entry 12)**

Following General Procedure 3, a React-IR cell was charged with CH₂Cl₂ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (10.2 mg) in CH₂Cl₂ (0.4 mL), and a solution of Me₂S in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol,
0.05 equiv). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 45% yield and a 5.8:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of (PhS)$_2$ (Table 2, entry 13)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.5 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (11.9 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of (PhS)$_2$ in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 2% yield was observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of n-Bu$_3$P=Se (Table 2, entry 14)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.0 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (11.8 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of n-Bu$_3$P=Se in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 9 min. After stirring for 1 h and quenching, 77% yield and an 8.5:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of (Me$_2$N)$_3$P=Se (Table 2, entry 15)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (34.9 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (10.7 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of (Me$_2$N)$_3$P=Se in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 4 min. After stirring for 1 h and quenching, 95% yield and a 4.6:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.
Iodolactonization of 1a in the Presence of (PhSe)$_2$ (Table 2, entry 16)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.0 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (10.4 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of (PhSe)$_2$ in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 15 min. After stirring for 1 h and quenching, 82% yield and a 10:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of $n$-Bu$_3$P (Table 2, entry 17)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.4 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (12.2 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of $n$-Bu$_3$P in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 52 min. After stirring for 2 h and quenching, 94% yield and a 5.1:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of (Me$_2$N)$_3$P (Table 2, entry 18)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.3 mg, 0.2 mmol, 1.0 equiv) and C$_6$Me$_6$ (10.2 mg) in CH$_2$Cl$_2$ (0.4 mL), and a solution of (Me$_2$N)$_3$P in CH$_2$Cl$_2$ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be 40 min. After stirring for 2 h and quenching, 53% yield and a 1.4:1 ratio of 2ab:3ab were observed by $^1$H NMR spectroscopy.

Iodolactonization of 1a in the Presence of I$_2$ (Table 2, entry 19)

Following General Procedure 3, a React-IR cell was charged with CH$_2$Cl$_2$ (1.0 mL), N-
iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (34.8 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (10.4 mg) in CH₂Cl₂ (0.4 mL), and a solution of I₂ in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 10% yield and a 24:1 ratio of 2ab:3ab were observed by ¹H NMR spectroscopy.

**Iodolactonization of 1a in the Presence of TFA (Table 2, entry 20)**

Following General Procedure 3, a React-IR cell was charged with CH₂Cl₂ (1.0 mL), N-iodosuccinimide (54 mg, 0.24 equiv), a solution of 1a (35.0 mg, 0.2 mmol, 1.0 equiv) and C₆Me₆ (11.1 mg) in CH₂Cl₂ (0.4 mL), and a solution of TFA in CH₂Cl₂ (0.1 mL, 0.1 M, 0.01 mmol, 0.05 equiv). The half-life was observed to be >180 min. After stirring for 3 h and quenching, 2ab and 3ab could not be observed by ¹H NMR spectroscopy.

**Iodolactonization of 1b. Preparation of rel-(5R)-Dihydro-5-[(R)-iodophenylmethyl]-2(3H)-furanone (3bb)¹²**

![Reaction Scheme]

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with N-iodosuccinimide (270 mg, 1.2 mmol, 1.2 equiv). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to -45 °C (CO₂/MeCN bath, internal temp). A solution of 1b (176.5 mg, 1.0 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) was added via cannula.
Next, a solution of (Me$_2$N)$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at -45 °C for 1 h, and then a solution of butyl vinyl ether in EtOH (2.5 mL, 1.2 M, 3.0 equiv) was added. After 5 min, sat. aq. Na$_2$S$_2$O$_3$ solution (5 mL) was added and the resulting biphasic mixture was allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ solution (20 mL) then were dried over MgSO$_4$, filtered, and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 3bb to 2bb was determined to be 24:1 by $^1$H NMR spectroscopy. The residue was purified by column chromatography (silica gel (37 g), 3 cm diam., hexane/EtOAc, 80:20) to provide a yellow light-sensitive solid, which was recrystallized from EtOAc/hexane (ca. 5 mL EtOAc at 23 °C, conc. in vacuo to ca. 3.5 mL, added 8 mL of hexane slowly, then cooled to -20 °C for 16 h) to provide 238.5 mg (79%) of 3bb as very light yellow plates.

Data for 3bb:

mp: 90 - 94 °C (dec.)

$^1$H NMR: (500 MHz, CDCl$_3$)

δ 7.52 – 7.40 (m, 2H, HC(Aryl)), 7.37 – 7.21 (m, 3H, HC(Aryl)), 5.12 (d, $J = 5.7$ Hz, 1H, HC(6)), 4.66 (td, $J = 7.3$, 5.5 Hz, 1H, HC(5)), 2.55 – 2.46 (m, 2H, H$_2$C(3)), 2.33 – 2.22 (m, 1H, HC(4)), 1.97 (dtd, $J = 13.3$, 9.4, 7.3 Hz, 1H, HC(4')).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

δ 175.6 (C(2)), 139.1 (C(7)), 128.9 (C(9/8)), 128.7 (C(10)), 128.4 (C(9/8)), 82.8 (C(5)), 34.2 (C(6)), 28.7 (C(3)), 26.9 (C(4)).
IR: (neat)

3064 (w), 2936 (m), 1778 (s), 1498 (m), 1456 (s), 1332 (m), 1296 (m), 1278 (m), 1176 (s), 1071 (m), 1049 (s), 1027 (s), 866 (m), 828 (m), 808 (m), 780 (s), 704 (s), 640 (s), 614 (m), 594 (m), 528 (w).

MS: (ESI)

129 (31), 157 (19), 175 (75), 303 (M + H$^+$, 100), 304 (15), 325 (55).

HRMS: Calculated: C$_{11}$H$_{12}$IO$_2$ (M + H$^+$, 302.9882; Found: 302.9879.

TLC: $R_f$ 0.13 (hexanes/EtOAc, 4:1) [UV]

Analysis: C$_{11}$H$_{11}$O$_2$ I (302.1)

Calcd:  C, 43.73;  H, 3.67;

Found:  C, 43.53;  H, 3.56;

Iodolactonization of 1c. Preparation of rel-(5R)-5-[(1'S)-1'-Iodo-2-methylpropyl]dihydro-2(3H)-furanone (3cb)

A 20-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with N-iodosuccinimide (270 mg, 1.2 mmol, 1.2 equiv). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to -45 °C (CO$_2$/MeCN bath, internal temp). A solution of 1c (142.0 mg, 1.0 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.0 mL) was added via cannula.
Next, a solution of Cy$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at -45 °C for 2 h, and then a solution of butyl vinyl ether in EtOH (2.5 mL, 1.2 M, 3.0 equiv) was added. After 10 min, sat. aq. Na$_2$S$_2$O$_3$ solution (5 mL) was added and the resulting biphasic mixture was allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ (25 mL), and then with brine (25 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 3cb to 2cb was determined to be 34:1 by $^1$H NMR spectroscopy. The residue was purified by column chromatography (silica gel (37 g), 3 cm diam., hexane/EtOAc, 80:20) to provide a colorless oil, which was diluted with hexane (ca. 0.5 mL) and seeded to provide 240.1 mg (90%) of 3cb as colorless needles.

**Data for 3cb:**

mp: 49 – 51 °C

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 4.61 (ddd, $J =$ 9.9, 8.2, 6.3 Hz, 1H, HC(5)), 4.08 (dd, $J =$ 10.0, 3.0 Hz, 1H, HC(6)), 2.67 – 2.48 (m, 3H, HC(3, 3’, 4), 2.07 – 1.94 (m, 1H, HC(4’)), 1.51 (heptd, $J =$ 6.5, 3.1 Hz, 1H, HC(7)), 0.97 (d, $J =$ 6.6 Hz, 3H, H$_3$C(9)), 0.92 (d, $J =$ 6.4 Hz, 3H, H$_3$C(8)).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

$\delta$ 176.5 (C(2), 80.6 (C(5)), 51.4 (C(6)), 30.0 (C(4)), 29.9 (C(7)), 29.0 (C(3)), 23.6 (C(9), 19.0 (C(8))).
IR: (KBr pellet)
2959 (s), 1768 (s), 1459 (s), 1427 (w), 1370 (m), 1339 (m), 1315 (m), 1302 (m),
1222 (m), 1167 (s), 1049 (m), 1017 (s), 990 (s), 912 (s), 870 (m), 822 (w), 802 (m),
691 (w), 636 (s), 539 (w), 529 (w).

MS: (ESI)
95 (30), 123 (30), 141 (100), 261 (12), 269 (15), 282 (52), 291 (M+ Na+, 100), 322.9
(15), 338.9 (17).

HRMS: Calculated: C$_8$H$_{13}$IO$_2$Na (M + Na$^+$) (290.9858); Found: 290.9859.

TLC: $R_f$ 0.28 (hexanes/EtOAc, 4:1) [UV/I$_2$/CAM]

Analysis: C$_8$H$_{13}$O$_2$I (268.1)

Calcd: C, 35.84; H, 4.89;
Found: C, 35.58; H, 4.78;

Stability of Iodolactones to Iodolactonization Conditions.

Iodolactonization of 1a under Thermodynamic Conditions$^{13}$. Preparation of rel-(5R)-
Dihydro-5-[(S)-iodophenylmethyl]-2(3H)-furanone (3ab)$^4$.

To a 10-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar was
added 1a (44 mg, 0.25 mmol, 1.0 equiv) and dry MeCN (2 mL) under argon. The flask was
cooled in an ice bath, charged with I$_2$ (190 mg, 0.75 mmol, 3.0 equiv) and wrapped in Al foil.
The reaction mixture was allowed to stir in the ice bath for 5.2 h, and then was quenched with saturated aq. Na$_2$S$_2$O$_3$ solution (10 mL). The resulting biphasic mixture was transferred to a 60-mL separatory funnel, where it was diluted with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ solution (5 mL), dried over MgSO$_4$, and concentrated in vacuo (23 °C, 10 mmHg) to provide a yellow solid. The residue was purified by column chromatography (silica gel (4 g), 1 cm diam., CH$_2$Cl$_2$) to provide 25.8 mg (34%) of 3ab. The spectroscopic data were in accordance with those described in the literature$^4$, and 2ab was not observable by $^1$H NMR spectroscopy.

**Stability of 3ab to Iodolactonization Conditions.**

To a flame-dried, 0.75-mL Schlenk flask, fitted with a septum and a magnetic stir bar, was added N-iodosuccinimide (9 mg, 0.04 mmol, 1.2 equiv). The flask was wrapped in Al foil, then was evacuated and filled with argon. The flask was cooled in a MeCN/CO$_2$, then was charged with 3ab (10.0 mg, 0.033 mmol, 1.0 equiv, >19:1 exo:endo) and the sides of the flask were rinsed with CH$_2$Cl$_2$ (0.1 mL). A solution of TFA in CH$_2$Cl$_2$ (0.025 mL, 0.066 M, 0.05 equiv), followed by a solution of $n$-Bu$_3$P=S in CH$_2$Cl$_2$ (0.025 mL, 0.066 M, 0.05 equiv). The reaction mixture was allowed to stir in the MeCN/CO$_2$ bath for 2 h, then was quenched with butyl vinyl ether in EtOH (0.081 mL, 1.2 M, 3.0 equiv), followed by sat. aq. Na$_2$S$_2$O$_3$ solution (0.5 mL). The resulting biphasic mixture was allowed to warm to room temperature, and was
transferred to a 60-mL separatory funnel where it was diluted with brine (5 mL) and was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). $^1$H NMR analysis showed a 40:1 ratio of 3ab to 2ab.

**Stability of 2ab to Iodolactonization Conditions.**

To a flame-dried, 0.75-mL Schlenk flask, fitted with a septum and a magnetic stir bar, was added N-iodosuccinimide (9 mg, 0.04 mmol, 1.2 equiv). The flask was wrapped in Al foil, then was evacuated and filled with argon. The flask was cooled in a MeCN/CO$_2$, then was charged with 2ab (10.0 mg, 0.033 mmol, 1.0 equiv, >19:1 endo:exo) and the sides of the flask were rinsed with CH$_2$Cl$_2$ (0.1 mL). A solution of TFA in CH$_2$Cl$_2$ (0.025 mL, 0.066 M, 0.05 equiv), followed by a solution of n-Bu$_3$P=S in CH$_2$Cl$_2$ (0.025 mL, 0.066 M, 0.05 equiv). The reaction mixture was allowed to stir in the MeCN/CO$_2$ bath for 2 h, then was quenched with butyl vinyl ether in EtOH (0.081 mL, 1.2 M, 3.0 equiv), followed by sat. aq. Na$_2$S$_2$O$_3$ solution (0.5 mL). The resulting biphasic mixture was allowed to warm to room temperature, and was transferred to a 60-mL separatory funnel where it was diluted with brine (5 mL) and was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo (23 °C, 10 mmHg). $^1$H NMR analysis showed a >19:1 ratio of 2ab to 3ab.
Lewis Base Catalyzed Iodocycloetherifications


A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with N-iodosuccinimide (270 mg, 1.2 mmol, 1.2 equiv). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to -45 °C (CO₂/MeCN bath, internal temp). A solution of 4a (162.2 mg, 1.0 mmol, 1.0 equiv) and TFA (3.8 µL, 0.05 mmol, 0.05 equiv) in CH₂Cl₂ (2.0 mL) was added via cannula. Next, a solution of n-Bu₃P=S in CH₂Cl₂ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at -45 °C for 2 h, and then a solution of butyl vinyl ether in EtOH (2.5 mL, 1.2 M, 3.0 equiv) was added. After 15 min, sat. aq. Na₂S₂O₃ solution (5 mL) and sat. aq. NaHCO₃ solution (5 mL) were added and the resulting biphasic mixture was allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with H₂O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ solution (25 mL) and brine (25 mL) then were dried over MgSO₄, filtered and concentrated in vacuo (23 °C, 10 mmHg). The ratio of 5ab to 6ab was determined to be 23:1 by ¹H NMR spectroscopy. The residue was purified by column chromatography (silica gel (36 g), 3 cm diam., hexane/EtOAc, 95:5) to provide 250.2 mg of 5ab as a light straw-colored oil. Further
purification by column chromatography (silica gel (19 g), 2 cm diam., hexane/EtOAc, 95:5) provided 215.7 mg (75%) of 5ab as a colorless oil.

Data for 5aa:

$^1$H NMR: (500 MHz, CDCl$_3$)

$\delta$ 7.42 – 7.29 (m, 5H), 4.44 (d, $J$ = 10.4 Hz, 1H, HC(2)), 4.28 – 4.16 (m, 2H, HC(3,6)), 3.70 (td, $J$ = 12.1, 2.1 Hz, 1H, HC(6’)), 2.79 – 2.64 (m, 1H, HC(4)), 2.35 (m, 1H, HC(4’)), 1.96 (m, 1H, HC(5)), 1.59 (dd, $J$ = 13.8, 2.2 Hz, 1H, HC(5’)).

$^{13}$C NMR: (125 MHz, CDCl$_3$)

$\delta$ 140.4 (C(7)), 128.5 (C(10)), 128.2 (C(8/9)), 127.5 (C(8/9), 86.3 (C(2)), 69.0 (C(6)), 38.5 (C(4)), 32.8 (C(3)), 29.7 (C(5)).

IR: (neat)

3064 (m), 3033 (s), 2943 (s), 2849 (s), 1494 (s), 1454 (s), 1372 (s), 1327 (m), 1308 (m), 1258 (s), 1214 (m), 1181 (m), 1140 (s), 1100 (s), 1020 (s), 960 (s), 933 (s), 906 (m), 880 (m), 846 (w), 820 (m), 755 (s), 697 (s), 636 (m), 533 (s), 519 (m).

MS: (EI, 70 eV)

51 (12), 55 (51), 56 (16), 57 (90), 60 (11), 61 (16), 67 (14), 69.0 (12), 69.1 (32), 70 (16), 71 (30), 73 (16), 77 (25), 78 (11), 79 (12), 81 (17), 82 (12), 83 (29), 85 (20.4), 90 (11), 91 (77), 92 (11), 95 (16), 96 (11), 97 (22), 105 (52), 107 (12), 109 (14), 111 (14), 115 (13), 129 (17), 134 (13), 149 (19), 154 (13), 161 (100), 162 (14), 176 (16), 177 (61), 234 (18), 259 (11), 260 (28), 281 (10), 288 (M$^+$, 4).

HRMS: Calculated: C$_{11}$H$_{13}$IO (M$^+$) (288.00115); Found: 287.99999.

TLC: $R_f$ 0.19 (hexanes/EtOAc, 19:1) [UV]
Analysis: C$_{11}$H$_{12}$O I (288.1)

Calcd: C, 45.85; H, 4.55;

Found: C, 46.09; H, 4.28;

Iodocycloetherification of 4b. Preparation of rel-(2S)-Tetrahydro-2-[(1’R)-1’-iodo-3-phenylpropyl]furan (6bb)

A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with N-iodosuccinimide (270 mg, 1.2 mmol, 1.2 equiv). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to -45 °C (CO$_2$/MeCN bath, internal temp). A solution of 4b (190.3 mg, 1.0 mmol, 1.0 equiv) and TFA (3.8 µL, 0.05 mmol, 0.05 equiv) in CH$_2$Cl$_2$ (2.0 mL) was added via cannula. Next, a solution of n-Bu$_3$P=S in CH$_2$Cl$_2$ (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at -45 °C for 2 h, and then a solution of butyl vinyl ether in EtOH (2.5 mL, 1.2 M, 3.0 equiv) was added. After 15 min, sat. aq. Na$_2$S$_2$O$_3$ solution (5 mL) and sat. aq. NaHCO$_3$ solution (5 mL) were added and the resulting biphasic mixture was allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with H$_2$O (25 mL) and was extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO$_3$ (25 mL) and brine (25 mL) then were dried over MgSO$_4$, filtered and
concentrated in vacuo (23 °C, 10 mmHg). The ratio of 6bb to 5bb was determined to be 35:1 by
1H NMR spectroscopy. The residue was purified by column chromatography (silica gel (36 g), 3
cm diam., hexane/EtOAc, 95:5) to provide 268.1 mg of a colorless oil, which was crystallized
from cold hexane (ca. 0.3 mL) to provide 253.8 mg of 6bb as colorless tabular crystals.

Data for 6bb:

mp: 28–30 °C

1H NMR: (500 MHz, CDCl3)

δ 7.28 (m, 2H, HC(10/11)), 7.21 (m, 3H, HC(12, 10/11)), 4.07 (ddd, J = 10.2, 7.1, 3.2
Hz, 1H, HC(6)), 3.92 (dd, J = 15.0, 7.2 Hz, 1H, HC(5)), 3.84 (td, J = 7.8, 5.5 Hz,
1H, HC(5′)), 3.76 (q, J = 7.1 Hz, 1H, HC(2)), 2.97 (ddd, J = 13.8, 9.1, 4.8 Hz, 1H,
HC(8)), 2.71 (ddd, J = 13.8, 9.0, 7.4 Hz, 1H, HC(8′)), 2.22 – 2.10 (m, 2H, HC(3, 7)),
2.05 (dtd, J = 14.7, 9.6, 4.8 Hz, 1H, HC(7′)), 1.99 – 1.82 (m, 2H, H2C(4)), 1.73 (ddd,
J = 16.2, 12.4, 8.1 Hz, 1H, HC(3′)).

13C NMR: (125 MHz, CDCl3)

δ 140.8 (C(9)), 128.5 (C(10/11)), 128.4 (C(10/11)), 126.0 (C(12)), 82.3 (C(2)), 68.9
(C(5)), 42.6 (C(6)), 38.0 (C(7)), 35.4 (C(8)), 32.2 (C(3)), 25.9 (C(4)).

IR: (neat)

3026 (m), 2945 (s), 2863 (m), 1603 (m), 1497 (m), 1454 (s), 1353 (m), 1182 (m),
1055 (s), 924 (m), 747 (s), 699 (s), 528 (m).

MS: (ESI)

199 (100), 200 (11), 287 (22), 317 (M + H⁺, 2).

TLC: Rf 0.20 (hexanes/EtOAc, 19:1) [UV]
Analysis: \( \text{C}_{13}\text{H}_{17}\text{OI} (316.2) \)

Calcd: \( \text{C}, 49.38; \text{H}, 5.42; \)

Found: \( \text{C}, 49.11; \text{H}, 5.38; \)

Iodocycloetherification of 4c. Preparation of rel-(2R)-Tetrahydro-2-[(1’R)-1’-iodo-3-phenylpropyl]furan (6cb)\(^6\)

A 50-mL, flame-dried Schlenk flask, fitted with a septum and a magnetic stir bar and wrapped in foil, was charged with \( \text{N}-\text{iodosuccinimide} (270 \text{ mg}, 1.2 \text{ mmol}, 1.2 \text{ equiv}) \). The flask was evacuated and filled with argon. Dichloromethane (5.0 mL) was added via syringe and then a thermocouple was fitted and the flask was cooled to \(-45 ^\circ \text{C} (\text{CO}_2/\text{MeCN} \text{ bath, internal temp})\). A solution of 4c (190.7 mg, 1.0 mmol, 1.0 equiv) and TFA (3.8 µL, 0.05 mmol, 0.05 equiv) in \( \text{CH}_2\text{Cl}_2 \) (2.0 mL) was added via cannula. Next, a solution of \( n-\text{Bu}_3\text{P=S} \) in \( \text{CH}_2\text{Cl}_2 \) (500 µL, 0.1 M, 0.05 equiv, 0.05 mmol) was added rapidly via syringe. The reaction mixture was stirred at \(-45 ^\circ \text{C} \) for 2 h, and then a solution of butyl vinyl ether in \( \text{EtOH} \) (2.5 mL, 1.2 M, 3.0 equiv) was added. After 20 min, sat. aq. \( \text{Na}_2\text{S}_2\text{O}_3 \) solution (5 mL) and sat. aq. \( \text{NaHCO}_3 \) solution (5 mL) were added and the resulting biphasic mixture was allowed to warm to room temperature. The reaction mixture was transferred to a 250-mL separatory funnel where it was diluted with \( \text{H}_2\text{O} \) (25 mL) and was extracted with \( \text{EtOAc} \) (3 x 25 mL). The combined organic extracts were washed with sat. aq. \( \text{NaHCO}_3 \) (25 mL) and brine (25 mL) then were dried over \( \text{MgSO}_4 \), filtered, and
concentrated in vacuo (23 °C, 10 mmHg). The residue was purified by column chromatography (silica gel (29 g), 3 cm diam., hexane/EtOAc, 95:5) to provide 255.1 mg (80%) of 6cb as a colorless oil.

Data for 6cb:

$^1$H NMR: (500 MHz, CDCl$_3$)

\[ \delta 7.34 - 7.25 \text{ (m, 2H, HC(Aryl))}, 7.21 \text{ (m, 3H, HC(Aryl))}, 4.04 \text{ (ddd, } J = 10.6, 4.5, 3.4 \text{ Hz, 1H, HC(6))}, 3.96 \text{ (dt, } J = 8.1, 6.8 \text{ Hz, 1H, HC(5))}, 3.83 \text{ (td, } J = 7.9, 5.8 \text{ Hz, 1H, HC(5'))}, 3.74 \text{ (ddd, } J = 8.0, 6.7, 4.7 \text{ Hz, 1H, HC(2))}, 2.97 \text{ (ddd, } J = 13.7, 8.9, 4.7 \text{ Hz, 1H, HC(8))}, 2.73 \text{ (ddd, } J = 13.8, 8.7, 7.7 \text{ Hz, 1H, HC(8'))}, 2.20 \text{ (ddd, } J = 15.1, 10.6, 8.9, 4.8 \text{ Hz, 1H, HC(7))}, 2.11 - 1.85 \text{ (m, 4H, HC(4, 4', 7', 3))}, 1.68 \text{ (dq, } J = 11.9, 8.0 \text{ Hz, 1H, HC(3'))}.

$^{13}$C NMR: (125 MHz, CDCl$_3$)

\[ \delta 140.8 \text{ (C(9))}, 128.6 \text{ (C(10/11))}, 128.5 \text{ (C(10/11))}, 126.1 \text{ (C(12))}, 82.4 \text{ (C(2))}, 69.0 \text{ (C(5))}, 41.6 \text{ (C(6))}, 37.9 \text{ (C(3/7/8))}, 35.6 \text{ (C(3/7/8))}, 30.9 \text{ (C(3/7/8))}, 26.2 \text{ (C(4))}.

References


