Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalysed ortho-Hydroxylative Phenol Dearomatization

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General

All reagents and solvents were supplied from Sigma-Aldrich, Fisher Scientific, Alfa Aesar or Fluorochem and were used without further purification. Compound purification by flash column chromatography was performed with Apollo Scientific 40-63 μm silica gel, or using automated flash chromatography (Teledyne ISCO CombiFlash), where crude mixtures were dry loaded. Melting points were measured in open capillary tubes using a Stuart scientific SMP3 melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254 plates and visualisation was achieved under UV as well as staining with KMnO₄ or vanillin. Infrared spectra (IR) were recorded using a Perkin-Elmer Spectrum 65 FT-IR spectrophotometer; samples were prepared as KBr discs. High Resolution Mass spectrometry (HRMS) was performed using a Thermo Scientific Exactive Orbitrap mass spectrometer. High performance liquid chromatography on a chiral stationary phase was performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector.

NMR spectra were recorded at 298 K using a Jeol ECZ 400 or 500 MHz spectrometer. ¹H, ¹³C and ¹⁹F spectra were recorded at 400/500 MHz, 101/126 MHz and 376 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual CDCl₃ or d₄-MeOH, and J values are given in Hertz (Hz). Abbreviations for multiplets are singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (td), heptet (hept), multiplet (m).

The chiral (S,S)-(+-)-acetonamine, (+)-(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine, was prepared according to Page.¹b Both the binaphthyl di-bromide and (S,S)-(+-)-acetonamine are also available from commercial sources.
Catalyst Synthesis

2-(2-bromoethyl)-benzaldehyde\(^{1a}\) (S1)

\[ \text{N-bromosuccinimide (3.18 g, 17.9 mmol) was added to a stirred solution of isochroman (1.87 mL, 14.9 mmol) in MeCN (15 mL) at r.t. The resulting suspension was then gradually heated to reflux for 2 h, before removing solvent in vacuo. EtOAc (ca. 15 mL) was then added, and the resulting suspension was filtered. The filtrate was then diluted with further EtOAc (100 mL), washed with 0.1 M NaOH (aq., 100 mL), followed by saturated brine solution (aq., 100 mL). The organic layer was then extracted, dried over MgSO}_{4}, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (0 → 5% v/v EtOAc in hexane) to yield the title compound as a pale-yellow oil (2.69 g, 85%). When not in use, samples were stored at -18 °C under N\(_2\).} \]

\[ \text{TLC R}_f: 0.5 (\text{Hexane/EtOAc 10:1).} \]

\[ \text{\(^{1H} \text{NMR (400 MHz, CDCl}_{3}\): } \delta 10.16 (s, 1H), 7.83 (dd, J = 7.5, 1.5 Hz, 1H), 7.57 (td, J = 7.5, 1.6 Hz, 1H), 7.49 (td, J = 7.5, 1.3 Hz, 1H), 7.36 – 7.33 (m, 1H), 3.65 – 3.55 (m, 4H).} \]

\[ \text{\(^{13C} \text{NMR (101 MHz, CDCl}_{3}\): } \delta 193.05, 140.65, 134.63, 134.02, 133.84, 132.24, 127.80, 36.42, 32.88.} \]

2,2'-biphenyldimethanol\(^{2}\) (S2)

\[ \text{NaBH}_4 (4.4 g, 115 mmol) was added to a stirred solution of diphenic acid (6.8 g, 28.0 mmol) in dry THF, (150 mL) at room temperature (20 °C), under N\(_2\). To the stirred suspension, a solution of I\(_2\) (14.6 g, 57.5 mmol) in dry THF (70 mL) was added dropwise at 0 °C via a pressure equalising dropping funnel, in approximately 20 min. The resulting mixture was then heated to reflux for 18 h, before cooling to 0 °C, and carefully quenching with MeOH (200 mL). Solvent was then removed in vacuo, followed by the addition of 20% w/v KOH (150 mL). The resulting suspension was then stirred for 1 h, before extracting with CH\(_2\)Cl\(_2\) (3 x 200 mL). The combined organic layers were then dried over MgSO\(_4\), filtered and concentrated in vacuo to afford an off-white solid of 2,2'-biphenyldimethanol (6.0 g, >99%) which required no further purification.} \]

\[ \text{\(^{1H} \text{NMR (400 MHz, CDCl}_{3}\): } \delta 7.46 (dd, J = 7.5, 1.1 Hz, 2H), 7.37 (td, J = 7.4, 1.4 Hz, 2H), 7.32 (td, J = 7.4, 1.4 Hz, 2H), 7.13 (dd, J = 7.4, 1.2 Hz, 2H), 4.38 – 4.24 (m, 2H), 3.30 (br s, 2H).} \]

\[ \text{\(^{13C} \text{NMR (101 MHz, CDCl}_{3}\): } \delta 140.11, 138.74, 129.76, 129.70, 128.19, 127.75, 62.83.} \]

\[ \text{LCMS (ESI\(^{+}\)): } \text{m/z calcd. for C}_{14}\text{H}_{14}\text{O}_{2} 237.1; \text{found 236.9 [M+Na].} \]
5,7-dihydrodibenzo[c,e]oxepine³ (S3)

\[
\text{2,2'-biphenyldimethanol (5.99 g, 28.0 mmol) was added to HBr (43 mL, 48% aq. solution) in H₂O (43 mL) at r.t., before heating to reflux for 1 h. The reaction mixture was then cooled to r.t., before diluting with Et₂O (200 mL). The aqueous layer was then separated, and washed with Et₂O (3 x 200 mL). The combined organics were then washed with sat. NaHCO₃ (150 mL) followed by sat. brine solution (150 mL). The organics were then dried over MgSO₄, filtered and concentrated in vacuo to afford a pale-yellow oil, which crystallised upon standing. The crude solid was then recrystallised from hexanes to afford the oxepine as an off-white solid (4.83 g, 88%). mp: 63-65 ⁰C.}
\]

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl₃):} & \quad \delta 7.57 (d, J = 7.3 Hz, 2H), 7.55 - 7.48 (m, 2H), 7.47 - 7.40 (m, 4H), 4.37 (s, 4H). \\
\text{13C NMR (126 MHz, CDCl₃):} & \quad \delta 141.35, 135.30, 129.84, 129.07, 128.40, 127.62, 67.68.
\end{align*}
\]

\[
\text{LCMS (ESI⁺): } m/z \text{ calcd. for C}_{14}H_{13}O 197.1; \text{ found 197.0 [M+H].}
\]

2-[2-(bromomethyl)phenyl]benzene carbaldehyde³ (S4)

\[
\text{NBS (5.29 g, 29.7 mmol) was added to a stirred solution of 5,7-dihydrodibenzo[c,e]oxepine (4.49 g, 22.9 mmol) in MeCN (90 mL). The resulting suspension was then heated to reflux for 4 h. The reaction was then cooled to r.t., before removing solvent in vacuo. The mixture was then suspended in EtOAc (ca. 25 mL) before filtering under suction. The filtrate was then diluted with further EtOAc (75 mL) and was washed with 0.1 M NaOH (100 mL), followed by sat. brine solution (100 mL). The organic layer was then extracted, dried over MgSO₄, filtered, and then concentrated in vacuo to afford an orange oil. The crude product was then purified by flash column chromatography (0 → 6% EtOAc in hexane) to furnish the title compound as a white solid (3.26 g, 52%). mp: 62-63 ⁰C.}
\]

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl₃):} & \quad \delta 9.74 (d, J = 0.8 Hz, 1H), 8.07 (dd, J = 7.8, 1.2 Hz, 1H), 7.67 (td, J = 7.5, 1.4 Hz, 1H), 7.61 - 7.53 (m, 2H), 7.47 - 7.34 (m, 3H), 7.21 (dd, J = 7.5, 1.2 Hz, 1H), 4.30 (dd, J = 40.9, 10.1 Hz, 2H). \\
\text{13C NMR (126 MHz, CDCl₃):} & \quad \delta 191.77, 143.39, 137.97, 136.09, 134.27, 133.67, 131.16, 130.83, 130.79, 129.17, 128.65, 128.47, 127.77, 31.47.
\end{align*}
\]

\[
\text{HRMS (ESI⁺): } m/z \text{ calcd. for C}_{14}H_{11}BrONa 296.9886; \text{ found 296.9885 [M+Na].}
\]
9-propyl-9-azatricyclo[9.4.0.0^2,7]pentadeca-1(11),2,4,6,8,12,14-heptaaen-9-iium bromide (2)

\[ \begin{array}{c}
\text{Br} \quad \text{O} \\
\text{EtOH, r.t.,} \quad 18 \text{ h} \\
\text{N} \quad \text{Pr} \\
\text{Br} \\
\end{array} \]

1-propylamine (0.25 mL, 3.04 mmol), was added dropwise to a stirred solution of 2-[2-(bromomethyl)phenyl]benzene carbaldehyde (1.00 g, 3.63 mmol) in EtOH (5 mL), at 0 °C. The reaction was then warmed to r.t., and stirred for 18 h. A mixture of hexane-Et\textsubscript{2}O was then added, causing the product to directly precipitate. The precipitate was filtered under suction, washing with further hexane and Et\textsubscript{2}O, to afford biphenylazepinium \( 2 \) as a white solid (871 mg, 91%).

\textbf{mp}: 120-122 °C.

\textbf{IR} \( \nu_{\text{max}} \) (cm\(^{-1}\), KBr disc): 2976, 2962, 2875, 1662.

\textbf{\( ^1\text{H NMR} \)} (400 MHz, CD\textsubscript{3}OD): \( \delta \) 9.33 (s, 1H), 8.08 (d, \( J = 7.9 \) Hz, 1H), 8.06 – 7.94 (m, 2H), 7.85 – 7.74 (m, 2H), 7.73 – 7.68 (m, 1H), 7.66 – 7.58 (m, 2H), 5.08 (s, 1H), 4.58 (s, 1H), 4.24 (s, 2H), 2.01 (s, 2H), 0.87 (t, \( J = 7.4 \) Hz, 3H).

\textbf{\( ^{13}\text{C NMR} \)} (101 MHz, CD\textsubscript{3}OD): \( \delta \) 170.90, 143.07, 138.41, 137.06, 135.72, 135.66, 131.67, 131.53, 131.30, 130.88, 130.06, 129.88, 128.05, 65.63, 57.07, 22.57, 10.62.

\textbf{HRMS (ESI\(^+\))}: \( m/z \) calcd. for C\(_{17}\)H\(_{18}\)N\(^+\) 236.1434; found 236.1434 [M+].

2,2-Dimethyl-4-phenyl-1,3-dioxan-5-amine

Methyl formate (0.2 mL, 3.3 mmol) and NaOMe (16 mg, 0.3 mmol) were added to a solution of the amino diol (500 mg, 3.0 mmol) in MeOH (5 mL). The resulting reaction mixture was then stirred for 3.5 h at r.t., before removing solvent \textit{in vacuo}. The residue was then dissolved in acetone (25 mL), before camphorsulfonic acid (70 mg, 0.3 mmol), and 2,2-dimethoxypropane (3.7 mL, 30 mmol) were added. The reaction mixture was then stirred for 4 h, at r.t., before removing solvents \textit{in vacuo}. The resulting oil was then redissolved in EtOAc (30 mL), before washing with sat. NaHCO\textsubscript{3} (30 mL). The organics were then dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The formamide was dissolved in hydrazine hydrate (50-60%, 20 mL), and then heated to reflux for 3 h. After cooling to room temperature (20 °C), the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were then washed with H\textsubscript{2}O (2 x 20 mL), dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The product was afforded as a pale-yellow oil (561 mg, 90% yield over 3 steps) and was used without further purification.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 – 7.23 (m, 5H), 5.09 (d, $J = 1.3$ Hz, 1H), 4.29 (dd, $J = 11.7$, 2.3 Hz, 1H), 3.89 (dd, $J = 11.7$, 1.8 Hz, 1H), 2.74 (q, $J = 2.0$ Hz, 1H), 1.53 (2 x s, 6H), 1.30 (br s, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 139.67, 128.50, 127.47, 125.78, 99.24, 73.91, 66.20, 49.81, 29.84, 18.69.

LCMS (ESI, m/z): calcd. for C$_{12}$H$_{17}$NO$_2$ 208.1; found 207.9 [M+H]+.

General Procedure A: Synthesis of Dihydroisoquinolinium and Biphenylazepinium Tetraphenylborate Salts 4a, 4b and 5

![Diagram of synthesis process]

The (S,S)-acetonamine (1.0 eq.) is added slowly to a solution of 2-(2-bromoethyl)-benzaldehyde S1 or 2-[2-(bromomethyl)phenyl]benzene carbaldehyde S4 (1.1 eq.) in absolute EtOH (1 mL mmol$^{-1}$), at 0 °C. The reaction mixture is then allowed to warm to room temperature (20 °C) and was stirred for 16 h, before adding NaBPh$_4$ (1.1 eq.) in a minimal amount of MeCN. The resulting precipitate is then filtered under suction, and washed with cold EtOH, H$_2$O, and Et$_2$O to afford the pure dihydroisoquinolinium or biphenylazepinium salt. Characterization for catalysts 4a-5 was consistent with the literature.$^{1a,1b}$

(R)-2′-(trifluoromethanesulfonyloxy)-[1,1′-binaphthalen]-2-yl trifluoromethanesulfonate$^{4,5}$ (S5)

![Diagram of triflate synthesis]

Tf$_2$O (8.8 mL, 52.5 mmol) was added dropwise, at 0 °C, to a solution of (R)-BINOL (5.00 g, 17.5 mmol), DMAP (855 mg, 7.0 mmol) and Et$_3$N (7.28 mL, 52.5 mmol), in dry CH$_2$Cl$_2$ (125 mL). The resulting reaction mixture was then stirred at rt for 1 h, before quenching with NaHCO$_3$ (250 mL). The organic layer was separated, and the aqueous layer was then washed with CH$_2$Cl$_2$ (3 x 250 mL). The combined organic extracts were then dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (10% EtOAc in hexane) to afford the triflate as a white solid (9.60 g, >99%).
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mp: 84-85 °C.

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.15 (d, $J = 9.1$ Hz, 2H), 8.01 (d, $J = 8.3$ Hz, 2H), 7.63 (d, $J = 9.1$ Hz, 2H), 7.61 – 7.57 (m, 2H), 7.43 – 7.40 (m, 2H), 7.28 – 7.25 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 145.53, 133.29, 132.49, 132.12, 128.49, 128.12, 127.46, 126.89, 123.58, 119.46, 118.21 (q, $J = 320.2$ Hz).

HRMS (ESI$^+$): $m/z$ calcd. for C$_{22}$H$_{12}$O$_6$S$_2$: 572.9872; found 572.9872 [M+Na].

(R)-2,2'-dimethyl-1,1'-binaphthalene$^{4,5}$ (S6)

![Chemical Structure](image)

To a flame dried 100 mL flask, MeMgBr (23.4 mL, 3.0 M in Et$_2$O) was added dropwise, at 0 °C, to the (R)-triflate (9.60 g, 17.4 mmol), and NiCl$_2$dppp (945 mg, 1.74 mmol) in dry Et$_2$O (100 mL). The resulting mixture was then stirred at r.t. for 18 h, before filtering the reaction through celite, and washing with copious CH$_2$Cl$_2$. The filtrate was then washed with 1M HCl (250 mL), followed by brine (250 mL). The organic layer was then dried, filtered, and concentrated in vacuo. The crude product was then purified by flash column chromatography (10% EtOAc in hexane) to afford the title compound as a colourless oil which solidified upon standing. (4.7 g, 96%).

mp: 68-71 °C.

$^1$H NMR (500 MHz CDCl$_3$): δ 7.91 (t, $J = 7.9$ Hz, 4H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.44 – 7.39 (m, 2H), 7.25 – 7.20 (m, 2H), 7.08 (d, $J = 8.5$ Hz, 2H), 2.07 (s, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 135.27, 134.43, 132.91, 132.36, 128.87, 132.91, 132.36, 128.87, 128.07, 127.58, 126.23, 125.79, 125.03, 20.18.

HRMS (ESI$^+$): $m/z$ calcd. for C$_{22}$H$_{18}$Na: 305.1301; found 305.1299 [M+Na].

(R)-2,2'-bis(bromomethyl)-1,1'-binaphthalene$^{4,5}$ (S7)

![Chemical Structure](image)

NBS (6.0 g, 33.7 mmol), was added to (R)-2,2'-dimethyl-1,1'-binaphthalene (4.3 g, 15.4 mmol), in CCl$_4$ (40 mL). AIBN (130 mg, 0.8 mmol) was then added, and the resulting mixture was then heated at reflux for 2 h. The reaction mixture was then cooled to r.t., and the resulting suspension was filtered under suction. The filtrate was concentrated in vacuo, before re-dissolving in EtOAc (100 mL). The organics were then washed with 0.1 M NaOH (2 x 100 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude product was purified by recrystallisation from CHCl$_3$/hexane, to afford the product as an off-white solid (3.8 g, 56%).
mp: 130-133 °C.

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.03 (d, $J = 8.6$ Hz, 2H), 7.94 (d, $J = 8.2$ Hz, 2H), 7.76 (d, $J = 8.6$ Hz, 2H), 7.52 – 7.48 (m, 2H), 7.31 – 7.24 (m, 2H), 7.09 (d, $J = 8.5$ Hz, 2H), 4.27 (s, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 134.32, 134.23, 133.40, 132.64, 129.51, 128.17, 127.89, 127.00, 126.96, 126.94, 32.78.

**General Procedure B: Binaphthylazepine synthesis**

![Chemical structure](image)

To a stirred suspension of the ($R$)-dibromide (1.00 eq.) and K$_2$CO$_3$ (3.00 eq.) in MeCN (50 mL per g dibromide), the chiral amine (1.00 eq.) was added dropwise, at room temperature (20 ºC). The resulting mixture was stirred at r.t. for 1 h, before heating at reflux for 18 h. The reaction was then cooled, and diluted with CH$_2$Cl$_2$. H$_2$O was added, and the organics were extracted with CH$_2$Cl$_2$ (x2). The combined organic extracts were then dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude products were purified by flash column chromatography to afford the desired azepine. Characterisation of the binaphthylazepines was consistent with the literature.$^6$-$^9$

**General Procedure C: Binaphthylazepinium tetraphenylborate synthesis**

![Chemical structure](image)

NBS (1.1 eq.) was added to a stirred solution of the azepine (1.0 eq.) in CH$_2$Cl$_2$ (50 mL per g of amine). The resulting solution was then stirred at r.t. until the amine is completely consumed (TLC, ~10 min), before removing CH$_2$Cl$_2$ in vacuo. The resulting residue is then dissolved in EtOH (30 mL per g amine), and NaBPh$_4$ (1.1 eq.) in the minimum volume of MeCN is then added slowly. The resulting mixture was stirred at r.t. for 15 minutes, before concentrating in vacuo. The crude product was then re-dissolved in CH$_2$Cl$_2$ (50 mL per g amine), and washed with H$_2$O (50 mL per g amine), followed by brine (50 mL per g amine). The organic layer was then dried over MgSO$_4$, filtered, and concentrated to afford the iminium salts as yellow-orange solids which were used without further purification. Characterisation of the binaphthylazepinium salts 6a-6h was consistent with the literature.$^6$-$^9$
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-
Hydroxylative Phenol Dearomatization

**Preparation of (R)-[(4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-yl]-3H-4-azepinium-cyclohepta[2,1-a;3,4-
a']dinaphthalene\textsuperscript{6,9} (8)**

Prepared according to general procedure B, using (+)-(4S,5S)-2,2-Dimethyl-4-phenyl-1,3-dioxan-5-
amine.\textsuperscript{1b} The crude product was purified by flash column chromatography (0 → 20% EtOAc in hexane),
to afford the title compound as a white solid in 68% yield.

**mp:** 122-124 °C.

\( ^1\text{H} \text{NMR (500 MHz, CDCl}_3): \delta \) 7.91 – 7.84 (m, 4H), 7.45 – 7.33 (m, 8H), 7.32 – 7.23 (m, 3H), 7.22 – 7.16 (m, 2H), 5.17 (d, J = 3.3 Hz, 1H), 4.23 (dd, J = 12.5, 3.7 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.93 (d, J = 12.2 Hz, 2H), 3.36 (d, J = 12.2 Hz, 2H), 2.72 (td, J = 3.5, 1.4 Hz, 1H), 1.71 (s, 3H), 1.62 (s, 3H).

\( ^{13}\text{C} \text{NMR (126 MHz, CDCl}_3): \) 140.43, 134.96, 134.77, 132.95, 131.36, 128.51, 128.22, 127.94, 127.72, 127.65, 126.87, 126.55, 125.53, 125.22, 99.41, 75.18, 65.98, 62.01, 59.97, 53.27, 29.94, 19.19.

**LCMS (ESI, m/z):** calcd. for C\textsubscript{34}H\textsubscript{31}NO\textsubscript{2} 486.2; found 486.2 [M+H]+.

\( \alpha \)\textsubscript{D}^25 = -241.1° (c = 1.05, acetone).

\( ^1\text{H} \text{NMR (400 MHz, } \text{d}_6\text{-DMSO): } \delta \) 9.15 (s, 1H), 8.23 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.49 – 7.33 (m, 4H), 7.29 – 7.14 (m, 11H), 7.05 (br s, 2H), 6.98 – 6.86 (m, 9H), 6.79 (t, J = 7.1 Hz, 4H), 5.89 (s, 1H), 5.81 (s, J = 10.3 Hz, 1H), 4.68 (dd, J = 13.4, 2.2 Hz, 1H), 4.59 (s, 1H), 4.30 – 4.15 (m, H), 1.79 (s, 3H), 1.74 (s, 3H).

\( ^{13}\text{C} \text{NMR (101 MHz, } \text{d}_6\text{-DMSO): } \delta \) 170.05, 164.09, 163.60, 163.11, 162.62, 160.39, 136.15, 135.53, 134.62, 134.51, 133.36, 131.34, 131.19, 130.64, 130.38, 130.12, 129.01, 128.88, 128.84, 128.63, 128.26, 127.66, 127.53, 127.49, 126.97, 126.62, 126.49, 125.81, 125.26, 125.24, 125.13, 124.89, 121.47, 100.23, 70.89, 66.19, 60.72, 29.33, 18.65.

**LCMS (ESI, m/z):** calcd. for C\textsubscript{34}H\textsubscript{30}NO\textsubscript{2} 484.2; found 484.1 [M+].
The title compound was prepared according to the procedure by Page. Iminium 6a (300 mg, 0.37 mmol), was dissolved in dry THF (50 mL). The resulting solution was cooled to -78 °C, before adding MeMgBr (1.24 mL, 3.0 M in Et₂O) dropwise. The reaction was kept at -78 °C for 1 h, before slowly allowing to warm to room temperature (20 °C) overnight. Sat. aq. NH₄Cl (50 mL) was then added to quench the reaction. THF was removed in vacuo, and then CHCl₃ (50 mL) was added. The organic layer was separated, before washing with H₂O (50 mL), followed by brine (50 mL). The organics were then dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash column chromatography (0 → 20% EtOAc in hexane) to afford the azepine as a white solid (165 mg, 89%).

The azepine was then dissolved in CH₂Cl₂ (5 mL), before adding NBS (54 mg, 0.30 mmol). The resulting solution was stirred at r.t. until the amine was completely consumed (TLC, 10 min), before removing CH₂Cl₂ in vacuo. EtOH (2 mL) was added, and NaBPh₄ (94.5 mg, 0.30 mmol) in MeCN (1 mL) was added slowly. The resulting mixture was stirred at r.t. for 15 minutes, before concentrating in vacuo. The crude product was re-dissolved in CH₂Cl₂ (15 mL), and washed with H₂O (15 mL), followed by brine (15 mL). The organic layer was then dried over MgSO₄, filtered, and concentrated to afford the iminium salt as an orange solid (230 mg, 76% over 2 steps). Characterisation of the azepine, and azepinium salt 6i was in agreement with the literature.
Substrate synthesis

General Procedure D: phenol α-benzyla\textit{tion}

The reactions were performed using an adapted, \textit{unoptimized} version of a procedure reported by Hori et al.\textsuperscript{10} Note: Newer, more reactive NaH was found to be \textit{detrimental} to the reaction.

To a vigorously stirred solution of the desired phenol (1.0 eq.) in dry toluene (2.5 mL mmol\textsuperscript{-1}), NaH (60% wt. dispersion in mineral oil, 1.5 eq.) is added at 0 °C. After ca. 20 minutes, the benzyl bromide (1.1 eq.) is added dropwise, before slowly allowing the reaction mixture to warm to room temperature (20 °C). The resulting suspension is then stirred vigorously for 18 h, before quenching with saturated NH\textsubscript{4}Cl. The organics are then extracted with EtOAc (x3), dried, filtered and concentrated \textit{in vacuo}. The crude products are then purified by flash column chromatography to afford the pure 2-benzyl phenols.

2-benzyl-6-methylphenol\textsuperscript{11} (S8)

Prepared from \textit{o}-cresol and benzyl bromide on a 9.2 mmol scale, to afford the product in 27% yield. Characterization was consistent with the literature.\textsuperscript{11}

6-benzyl-2,3-dimethylphenol (S9)

Prepared from 2,3-dimethylphenol and benzyl bromide on a 4.1 mmol scale, to afford the product in 20% yield.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta 7.33 – 7.28 & \text{ (m, 2H)}, 7.25 – 7.19 \text{ (m, 3H)}, 6.90 \text{ (d, } J = 7.6 \text{ Hz, 1H)}, 6.74 \text{ (d, } J = 7.6 \text{ Hz, 1H}), 4.60 \text{ (s, 1H)}, 3.98 \text{ (s, 2H)}, 2.28 \text{ (s, 3H)}, 2.15 \text{ (s, 3H)}.
\end{align*}

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}):
\begin{align*}
\delta 152.08, 139.94, 136.56, 128.88, 128.73, 127.73, 126.60, 123.93, 122.79, 122.13, 37.04, 20.22, 11.80.
\end{align*}

HRMS (ESI\textsuperscript{+}): \textit{m/z} calcd. for C\textsubscript{16}H\textsubscript{16}ONa 235.1093; found 235.1093 [M+Na].
2,3-dimethyl-6-[(4-methylphenyl)methyl]phenol (S10)

Prepared from 2,3-dimethylphenol and 4-methylbenzyl bromide on a 2.5 mmol scale, to afford the product in 47% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16 – 7.09 (m, 4H), 6.91 (d, $J$ = 7.6 Hz, 1H), 6.74 (d, $J$ = 7.6 Hz, 1H), 4.67 – 4.62 (m, 1H), 3.94 (s, 2H), 2.33 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 152.14, 136.68, 136.51, 136.21, 129.62, 128.59, 127.65, 124.08, 122.90, 122.05, 36.75, 21.15, 20.20, 11.78.

HRMS (ESI$^+$): m/z calcd. for C$_{16}$H$_{18}$ONa 249.1250; found 249.1250 [M+Na].

6-[(4-fluorophenyl)methyl]-2,3-dimethylphenol (S11)

Prepared from 2,3-dimethylphenol and 4-fluorobenzyl bromide on a 4.1 mmol scale, to afford the product in 48% yield.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 – 7.17 (m, 2H), 7.02 – 6.95 (m, 2H), 6.89 (d, $J$ = 7.6 Hz, 1H), 6.76 (d, $J$ = 7.6 Hz, 1H), 4.60 (s, $J$ = 2.5 Hz, 1H), 3.95 (s, 2H), 2.29 (s, 3H), 2.16 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 162.89, 160.46, 151.92, 136.59, 135.83, 135.80, 130.18, 130.10, 127.62, 123.97, 122.55, 122.23, 115.63, 115.42, 36.05, 20.23, 11.77.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -116.76 – -116.86 (m).

HRMS (ESI$^+$): m/z calcd. for C$_{15}$H$_{15}$FONa 253.0999; found 253.0999 [M+Na].
Optimisation of the synthesis of (±)-bis(2,6-xylenol)

\[
\begin{align*}
\text{MeOH} & \quad \text{Me} \\
\text{Me} & \quad \text{OH} & \quad \text{Me} \\
& \quad \text{OH} & \quad \text{Me}
\end{align*}
\]

1a

2 (10 mol\%)

\[
\begin{align*}
\text{H}_2\text{O}_2 & \quad \text{1:1 co-solvent-H}_2\text{O} \\
\text{base} & \quad 0 \to 20 \degree\text{C}, 18 \text{ h}
\end{align*}
\]

(±)-bis(2,6-xylenol) 3a

[X-ray structure]

| Entry | Solvent            | Base  | \(\text{H}_2\text{O}_2\) eq. | Yield  |
|-------|--------------------|-------|-----------------------------|--------|
| 1a    | MeCN-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 1.5                          | 17%    |
| 2     | MeCN-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 2.0                          | 34%    |
| 3     | MeCN-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 3.0                          | 65%    |
| 4     | MeCN-H\(_2\)O (1:1) | NaOH  | 3.0                          | < 5%   |
| 5     | MeOH-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 3.0                          | < 10%  |
| 6     | CH\(_2\)Cl\(_2\)-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 3.0                          | < 5%   |
| 7     | THF-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 3.0                          | < 5%   |
| 8     | PhCN-H\(_2\)O (1:1) | Na\(_2\)CO\(_3\) | 3.0                          | 55%    |
| 9     | MeCN-H\(_2\)O (1:1) | none  | 3.0                          | < 5%   |
| 10    | MeCN-H\(_2\)O (9:1)| Na\(_2\)CO\(_3\) | 3.0                          | < 5%   |

Table S1. Optimization of the racemic synthesis of 3a. Reactions performed on a 0.4 mmol scale. *2.5 mmol. †Used as a 30% aq. solution. ‡Isolated yields after chromatography. ‡‡h reaction time.
## Extended optimisation of the enantioselective phenol dearomatization reaction

![Chemical structure](image)

| Entry | Oxidant<sup>a</sup> | Solvent | Catalyst | T (°C) | Yield | e.r.<sup>c</sup> |
|-------|----------------------|---------|----------|--------|-------|-----------------|
| 1     | H₂O₂                 | MeCN-H₂O (1:1) | 4a | 20 °C | 80% | 79:21 |
| 2     | H₂O₂                 | MeCN-H₂O (1:1) | 5 | 20 °C | 90% | 60:40 |
| 3     | Oxone                | MeCN-H₂O (1:1) | 4a | 20 °C | 14% | 76:24 |
| 4     | H₂O₂                 | MeCN-H₂O (1:1) | 4b | 20 °C | 96% | 79:21 |
| 5     | H₂O₂                 | MeCN-H₂O (1:1) | 4a | 0 °C | 91% | 85.5:14.5 |
| 6     | UHP/PhSe₂<sup>b</sup> | CHCl₃ | 4a | 0 °C | 52% | 88:12 |
| 7     | H₂O₂                 | MeCN-H₂O (1:1) | 6a | 0 °C | 75% | 95:5 |
| 8     | UHP/PhSe₂<sup>b</sup> | CHCl₃ | 6a | 0 °C | 53% | 87:13 |
| 9     | H₂O₂                 | MeCN-H₂O (1:1) | 6b | 0 °C | 56% | 10:90 |
| 10<sup>c</sup> | H₂O₂             | MeCN-H₂O (1:1) | 6a | 0 °C | 40% | 91:9 |
| 11<sup>d</sup> | H₂O₂             | MeCN-H₂O (2:1) | 7 | 0 °C | 29% | 42:58 |
| 12    | H₂O₂                 | MeCN-H₂O (1:1) | 6c | 0 °C | 74% | 88:12 |
| 13    | H₂O₂                 | MeCN-H₂O (1:1) | 6d | 0 °C | 42% | 79:21 |
| 14    | H₂O₂                 | MeCN-H₂O (1:1) | 6e | 0 °C | 53% | 84:16 |
| 15    | H₂O₂                 | MeCN-H₂O (1:1) | 6f | 0 °C | 49% | 74:26 |
| 16    | H₂O₂                 | MeCN-H₂O (1:1) | 6g | 0 °C | 61% | 79:21 |
| 17    | H₂O₂                 | MeCN-H₂O (1:1) | 6h | 0 °C | 69% | 95:5 |

### Table S2
Extended optimization of the enantioselective o-HPD-[4+2] reaction. All reactions performed on an 0.4 mmol scale.<sup>a</sup>

- 3.0 eq. H₂O₂, 5 mol% PhSe₂.  
- Measured by chiral stationary phase HPLC.  
- Performed at pH = 10 using Na₂CO₃-NaHCO₃ buffer.  
- Employed using Shi’s reported conditions: substrate (0.5 mmol), MeCN (1 mL), 0.5 mL 1.0 M K₂CO₃ in 0.4 mM EDTA, H₂O₂ (1.5 mmol), 30 mol% D-epoxone (Shi catalyst).
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

Figure S1. Screened chiral catalysts
General Procedure E for the preparation of racemic compounds

To a stirred mixture of the phenol (0.41 mmol), catalyst 2 (10 or 20 mol%), and Na$_2$CO$_3$ (2.46 mmol) in 1:1 MeCN-H$_2$O (2.5 mL), H$_2$O$_2$ (126 μL, 30% aq. soln) was added at 0 ⁰C. The resulting mixture was then warmed to room temperature (20 ⁰C) and stirred overnight, before quenching the peroxide with Na$_2$S$_2$O$_3$. The reaction was then diluted with CH$_2$Cl$_2$, and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organics were then dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification was achieved using flash column chromatography.

**Note:** Where stated, preparative TLC was performed to obtain a racemic sample suitable for HPLC. In general, reactions perform considerably better with chiral catalysts 4a-6a.

**Figure S2.** Representative Combiflash trace for the tandem HPD-[4+2] cycloaddition using 2, exemplified for the dearomatization of 2,6-dimethylphenol. tR = 9.5 min corresponds to the bicyclo[2.2.2]octenone product.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

General Procedure F for the enantioselective phenol dearomatization reactions

To a stirred mixture of the phenol (0.41 mmol), catalyst 6a (10 mol%), and Na₂CO₃ (2.46 mmol) in 1:1 MeCN-H₂O (2.5 mL) at 0 °C, H₂O₂ (126 μL, 30% aq. soln) was added. The resulting mixture was then stirred overnight at 0 °C, before quenching the peroxide with Na₂S₂O₃. The reaction was then diluted with CH₂Cl₂ and extracted with CH₂Cl₂ (2 x 15 mL). The combined organics were then dried over MgSO₄, filtered, and concentrated in vacuo. Purification was achieved using flash column chromatography.

Figure S3. Representative Combiflash trace for the tandem HPD-[4+2] cycloaddition using chiral catalyst 6a, exemplified for the dearomatization of 2,6-dimethylphenol. tᵣ = 9.5 min corresponds to the bicyclo[2.2.2]octenone product

Figure S4. Representative TLC (1:1 hexane:EtOAc) for the o-HPD-[4+2] reaction of 2,6-dimethylphenol. (a) short wave UV visualisation (b) vanillin staining highlights the product.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

(+)-bis(2,6-xylenol)$^{12,13}$ (+)-3a

The racemic material was prepared according to general procedure E. The crude product was purified by automated flash column chromatography (0 → 80% EtOAc in hexane) to yield the title compound as a white solid (37 mg, 66%). Chiral HPLC achieved with Chiralpak IC column (75:25 Hexane:IPA) $t_R = 12.5$ min (enantiomer 1), 21.5 min (enantiomer 2). Flow rate 0.75 mL min$^{-1}$.

The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (42 mg, 75% yield, 95:5 e.r.).

mp: 171-173 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.30 – 6.23 (m, 2H), 5.51 (dd, $J = 8.1$, 0.9 Hz, 1H), 4.01 (s, 1H), 3.38 (dt, $J = 6.8$, 1.7 Hz, 1H), 3.25 (dd, $J = 8.4$, 2.0 Hz, 1H), 2.87 (dd, $J = 6.9$, 5.1 Hz, 1H), 2.40 (s, 1H), 1.85 (t, $J = 1.4$ Hz, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 214.99, 203.15, 139.43, 135.91, 135.50, 133.38, 73.80, 73.08, 53.89, 44.37, 43.81, 42.87, 31.90, 26.38, 16.52, 15.80.

LCMS (ESI$^+$): m/z calcd. for C$_{16}$H$_{20}$O$_4$ 277.1; found 276.9 [M+H].

$\left[\alpha\right]_{D}^{25} = +113.5^o$ (c = 0.16, CHCl$_3$).
The enantioselective reaction was achieved according to general procedure F, using catalyst \textit{ent-6a}. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (44.5 mg, 78% yield, 94:6 e.r.). Analytical data was identical to that described for (+)-bis(2,6-xylenol).
8,10-dihydroxy-2,4,4a,6,8,10-hexamethyl-4,4a,8a-tetrahydro-1,4-ethanonaphthalene-7,9(1H)-dione (3b)

Prepared using general procedure E from 2,4,6-trimethylphenol (55.8 mg, 0.41 mmol). The crude product was purified by automated flash column chromatography (0 → 50% EtOAc in hexane) to yield the title compound as a white solid (41 mg, 66%). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) t_R = 8.3 min (enantiomer 1), 9.7 min (enantiomer 2). Flow rate 0.75 mL min^{-1}. The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (49 mg, 79% yield, 95:5 e.r.).

mp: 166-168 °C.

^1H NMR (400 MHz, CDCl_3): δ 6.02 (s, 1H), 5.08 – 5.00 (m, 1H), 3.93 (s, 1H), 3.14 (t, J = 2.0 Hz, 1H), 2.80 (d, J = 1.9 Hz, 1H), 2.31 (s, 1H), 1.83 (d, J = 1.4 Hz, 3H), 1.70 (d, J = 1.6 Hz, 3H), 1.36 (s, 3H), 1.24 (s x2, 6H), 1.16 (s, 3H).

^13C NMR (101 MHz, CDCl_3): δ 214.26, 202.61, 145.39, 145.23, 133.22, 127.73, 73.87, 72.39, 57.88, 48.86, 48.77, 45.50, 32.59, 25.34, 23.33, 21.59, 16.39, 12.58.

LCMS (ESI+): m/z calcd. for C_{18}H_{24}O_4 305.2; found 305.0 [M+H].
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

3,5,8,10-tetraethyl-3,10-dihydroxytricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3c)

The racemic material was prepared using general procedure E from 2,6-diethylphenol (0.41 mmol). Prep. TLC was performed on the crude product using 7:3 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) t<sub>R</sub> = 8.5 min (enantiomer 1), 12 min (enantiomer 2). Flow rate 0.75 mL min<sup>-1</sup>

The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (53.5 mg, 79% yield, 98:2 e.r.).

mp: 90-92 °C.
IR (cm<sup>-1</sup>): 3434, 2970, 2932, 1727, 1672.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.26 (dd, <i>J</i> = 8.2, 6.8 Hz, 1H), 6.19 (d, <i>J</i> = 4.3 Hz, 1H), 5.58 (dd, <i>J</i> = 8.3, 1.3 Hz, 1H), 4.00 (s, 1H), 3.38 (dt, <i>J</i> = 6.8, 1.7 Hz, 1H), 3.13 (dd, <i>J</i> = 8.2, 1.8 Hz, 1H), 2.96 (dd, <i>J</i> = 8.2, 4.3 Hz, 1H), 2.44 – 2.10 (m, 3H), 1.95 – 1.68 (m, 2H), 1.62 (q, <i>J</i> = 7.4 Hz, 2H), 1.53 – 1.32 (m, 2H), 1.05 – 0.94 (m, 6H), 0.87 (t, <i>J</i> = 7.5 Hz, 3H), 0.66 (t, <i>J</i> = 7.4 Hz, 3H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 215.98, 203.02, 141.61, 137.89, 134.31, 132.23, 76.90, 76.31, 58.48, 44.44, 42.28, 41.46, 37.07, 29.92, 23.29, 22.42, 12.79, 9.54, 7.38, 7.05.

HRMS (ESI<sup>+</sup>): m/z calcd. for C<sub>20</sub>H<sub>33</sub>O<sub>4</sub>Na 355.1880; found 355.1879 [M+Na].
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

3,10-Dihydroxy-3,5,6,8,10,12-hexamethyltricyclo[6.2.2.02,7]dodeca-5,11-diene-4,9-dione \(^{12}\) (3d)

The racemic material was prepared according to procedure E, from 2,3,6-trimethylphenol (55.8 mg, 0.41 mmol). The crude mixture was purified by automated flash column chromatography (0 → 80% EtOAc in hexane) to yield the title compound as an off-white solid (42.6 mg, 68%). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) \( t_R = 12 \) min (enantiomer 1), 25 min (enantiomer 2). Flow rate 0.75 mL min\(^{-1}\).

The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (45 mg, 72% yield, 97:3 e.r.).

**mp:** 179-181 °C.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 5.97 (dd, \( J = 6.9, 1.4 \) Hz, 1H), 4.13 (s, 1H), 3.34 (dd, \( J = 6.9, 2.7 \) Hz, 1H), 2.99 (dd, \( J = 8.6, 2.6 \) Hz, 1H), 2.88 (d, \( J = 8.6 \) Hz, 1H), 2.28 (s, 1H), 1.99 (d, \( J = 0.8 \) Hz, 3H), 1.83 – 1.80 (m, 3H), 1.45 (d, \( J = 1.6 \) Hz, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 213.90, 202.95, 148.43, 137.09, 132.45, 131.21, 73.82, 72.11, 56.55, 49.12, 44.30, 41.40, 32.20, 26.37, 23.75, 18.80, 15.27, 13.66.

**LCMS (ESI\(^+\)):** \( m/z \) calcd. for C\(_{18}\)H\(_{24}\)O\(_4\) 305.2; found 305.0 [M+H].

![Graph](image-url)
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

(3R)-3,10-dibenzyl-3,10-dihydroxy-5,6,8,12-tetramethyltricyclo[6.2.2.0²,⁷]dodeca-5,11-diene-4,9-dione (3e)

The racemic material was prepared using general procedure E from 2-benzyl-5,6-dimethyl phenol (0.28 mmol). Prep. TLC was performed on the crude product using 2:1 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (60:40 Hexane:IPA) t_R = 10 min (enantiomer 1), ca. 28 min (enantiomer 2). Flow rate 0.75 mL min⁻¹.

The enantioselective reaction was achieved according to general procedure F (0.37 mmol). The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (61.7 mg, 73% yield, 97:3 e.r.).

**mp:** 64-65 °C

**IR (cm⁻¹):** 3446, 3027, 2918, 2851, 1720, 1670.

**¹H NMR (400 MHz, CDCl₃):** δ 7.35 – 7.27 (m, 3H), 7.18 – 7.13 (m, 5H), 6.94 – 6.89 (m, 2H), 5.95 (dd, J = 6.9, 1.5 Hz, 1H), 4.10 (s, 1H), 3.25 (dd, J = 6.9, 2.4 Hz, 1H), 3.05 (dd, J = 8.5, 2.4 Hz, 1H), 2.96 (d, J = 8.5 Hz, 1H), 2.83 (d, J = 3.0 Hz, 1H), 2.80 (d, J = 3.4 Hz, 1H), 2.71 (d, J = 13.9 Hz, 1H), 2.64 (d, J = 13.4 Hz, 1H), 2.22 (s, 1H), 1.99 (d, J = 0.9 Hz, 3H), 1.67 – 1.65 (m, 3H), 1.45 (d, J = 1.6 Hz, 3H), 1.31 (s, 3H).

**¹³C NMR (126 MHz, CDCl₃):** δ 213.26, 200.72, 148.66, 137.21, 135.75, 135.54, 132.02, 131.77, 130.50, 129.96, 128.58, 128.13, 127.23, 126.98, 77.27, 74.57, 57.08, 51.38, 50.63, 43.68, 41.58, 40.78, 23.76, 18.92, 15.56, 13.62.

**HRMS (ESI⁺):** m/z calcd. for C₃₀H₃₂O₄Na 479.2192; found 479.2193 [M+Na].

**Note:** The second enantiomer has a very broad peak in the HPLC chromatogram. Alternative chiral stationary phases and eluents were unsuccessful in separating the enantiomers.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

(3R)-3,10-dihydroxy-5,6,8,12-tetramethyl-3,10-bis[(4-methylphenyl)methyl]tricyclo[6.2.2.02,7]dodeca-5,11-diene-4,9-dione (3f)

The racemic material was prepared using general procedure E. Prep. TLC was performed on the crude product using 2:1 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) tR = 19 min (enantiomer 1), 36.5 min (enantiomer 2). Flow rate 0.75 mL min⁻¹.

The enantioselective reaction was achieved according to general procedure F (0.26 mmol). The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (45 mg, 70% yield, 96:4 e.r.).

**mp:** 148-149 °C  
**IR (cm⁻¹):** 3388, 3018, 2939, 2923, 1717, 1667.

**¹H NMR (400 MHz, CDCl₃):** δ 7.12 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 7.9 Hz, 2H), 5.97 (dd, J = 6.9, 1.3 Hz, 1H), 4.08 (s, 1H), 3.24 (dd, J = 6.9, 2.4 Hz, 1H), 3.03 (dd, J = 8.5, 2.3 Hz, 1H), 2.95 (d, J = 8.5 Hz, 1H), 2.77 (d, J = 13.7 Hz, 2H), 2.66 (d, J = 13.9 Hz, 1H), 2.60 (d, J = 13.5 Hz, 1H), 2.33 (s, 3H), 2.26 (s, 3H), 2.18 (s, 1H), 1.99 (s, 3H), 1.67 (s, 3H), 1.46 (d, J = 1.4 Hz, 3H), 1.30 (s, 3H).

**¹³C NMR (126 MHz, CDCl₃):** δ 213.31, 200.86, 148.60, 137.17, 136.81, 136.44, 132.60, 132.30, 131.97, 131.84, 130.35, 129.81, 129.32, 128.85, 77.34, 74.51, 57.09, 51.01, 50.63, 43.21, 41.58, 40.73, 23.76, 21.23, 21.19, 18.93, 15.58, 13.63.

**HRMS (ESI⁺):** m/z calcd. for C₃₂H₃₆O₄Na 507.2506; found 507.2506 [M+Na].
(3R)-3,10-bis[(4-fluorophenyl)methyl]-3,10-dihydroxy-5,6,8,12-tetramethyltricyclo[6.2.2.0^2,7]dodeca-5,11-diene-4,9-dione (3g)

The racemic material was prepared using general procedure E. Prep. TLC was performed on the crude product using 2:1 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) t_R = 10 min (enantiomer 1), 27.5 min (enantiomer 2). Flow rate 0.75 mL min^-1.

The enantioselective reaction was achieved according to general procedure F (0.26 mmol). The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (61 mg, 98:2 e.r.). The product was found to be inseparable from a catalyst decomposition product (~10% by ^1H NMR) by chromatography. To further purify the title compound, the product was recrystallised in a screw cap vial, using 4:1 hexane-EtOAc. The crystals were isolated by careful decantation by pipette, before drying in vacuo. This afforded the title compound as colourless crystals, in 69% overall yield (73% mass recovery from crystallisation). The enantiopurity of the recrystallised material was unchanged.

mp: 126-128 °C
IR (cm^-1): 3416, 3054, 2916, 1717, 1667.

^1H NMR (400 MHz, CDCl_3): δ 7.14 – 7.09 (m, 2H), 7.02 – 6.97 (m, 2H), 6.89 – 6.85 (m, 4H), 5.92 (dd, J = 6.9, 1.4 Hz, 1H), 4.07 (s, 1H), 3.20 (dd, J = 6.9, 2.3 Hz, 1H), 3.01 (dd, J = 8.6, 2.2 Hz, 1H), 2.96 (d, J = 8.5 Hz, 1H), 2.79 (d, J = 9.5 Hz, 1H), 2.76 (d, J = 10.0 Hz, 1H), 2.66 (d, J = 14.1 Hz, 1H), 2.60 (d, J = 13.6 Hz, 1H), 2.20 (s, 1H), 2.03 (s, 3H), 1.67 (s, 3H), 1.46 (d, J = 1.5 Hz, 3H), 1.31 (s, 3H).

^13C NMR (126 MHz, CDCl_3): δ 213.32, 200.61, 163.47, 163.26, 161.03, 160.82, 148.67, 137.40, 131.93, 131.85, 131.50, 131.39, 131.31, 131.24, 115.48, 115.27, 115.09, 114.88, 74.52, 57.09, 50.61, 50.34, 42.82, 41.42, 40.71, 23.80, 18.93, 15.52, 13.61.

^19F NMR (376 MHz, CDCl_3): δ -115.70 – -115.79 (m), -115.80 – -115.90 (m).
HRMS (ESI^+): m/z calcd. for C_30H_30F_2O_4Na 515.2004; found 515.2004 [M+Na].
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

3,10-dihydroxy-3,10-diisopropyl-6,12-dimethyltricyclo[6.2.2.0²7]dodeca-5,11-diene-4,9-dione¹²

(3h)

The racemic material was prepared using general procedure E from 2-isopropyl-5-methylphenol (0.41 mmol). Chiral HPLC was achieved with Chiralpak IC column (95:5 Hexane:IPA) $t_R = 19$ min (enantiomer 1), 23 min (enantiomer 2). Flow rate 0.75 mL min⁻¹. The enantioselective reaction was achieved according to a modified version of general procedure F, in which the reaction was performed at room temperature (20 °C). The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (47.1 mg, 69% yield, >99:1 e.r.).

mp: 163-165 °C.

¹H NMR (500 MHz, CDCl₃): $\delta$ 6.00 – 5.99 (m, 1H), 5.86 – 5.83 (m, 1H), 3.79 (d, $J = 3.8$ Hz, 1H), 3.31 (dd, $J = 6.8$, 1.8 Hz, 1H), 3.27 (dd, $J = 8.2$, 1.5 Hz, 1H), 3.18 (dd, $J = 2.7$, 1.9 Hz, 1H), 3.09 (dd, $J = 8.2$, 2.7 Hz, 1H), 2.23 (s, 1H), 1.97 (s, 3H), 1.78 (hept, $J = 6.8$ Hz, 1H), 1.63 – 1.57 (m, 4H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.59 (d, $J = 6.7$ Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): 215.01, 201.95, 156.06, 135.96, 126.81, 125.58, 78.37, 77.99, 57.41, 47.41, 42.08, 37.48, 37.41, 32.66, 22.27, 21.52, 16.89, 16.79, 16.45, 16.22.

LCMS (ESI⁺): $m/z$ calcld. for C₂₀H₂₉O₄ 333.2; found 333.0 [M+H].

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[Image of HPLC charts]
3,10-dihydroxy-3,6,10,12-tetramethyltricyclo[6.2.2.0²,7]dodeca-5,11-diene-4,9-dione¹² (3k)

The racemic material was prepared using general procedure E from 2,5-dimethylphenol (0.41 mmol). Prep. TLC was performed on the crude product using 1:1 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) tᵣ = 13 min (enantiomer 1), 26 min (enantiomer 2). Flow rate 0.75 mL min⁻¹

The enantioselective reaction was achieved according to a modified version of general procedure F, in which the reaction was performed at room temperature (20 °C). The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (22.5 mg, 40% yield, 93:7 e.r.).

mp: 188–190 °C.

¹H NMR (500 MHz, CDCl₃): δ 6.02 (s, 1H), 5.89 – 5.85 (dt, J = 6.7 Hz, 1.63 Hz, 1H), 3.99 (s, 1H), 3.32 (dd, J = 6.8, 1.9 Hz, 1H), 3.18 – 3.14 (m, 3H), 2.23 (s, 1H), 2.00 (d, J = 1.3 Hz, 3H), 1.62 (d, J = 1.7 Hz, 3H), 1.30 (s, 3H), 1.25 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 212.91, 201.55, 156.47, 136.68, 128.50, 125.06, 73.30, 73.17, 57.11, 44.92, 44.43, 41.31, 32.15, 26.08, 22.57, 21.62.

LCMS (ESI⁺): m/z calcd. for C₁₆H₂₀O₄ 277.1 found 276.9 [M+H].

![MS Spectrum](image1.png)

![MS Spectrum](image2.png)
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed 
Ortho-Hydroxylative Phenol Dearomatization

(+)·biscarvacrol (+)·3\(\text{I}^{12,14}\)

The racemic material was prepared using general procedure E from 2-methyl-5-isopropylphenol (61.5 mg, 0.41 mmol). The crude mixture was purified by automated flash column chromatography (0 → 80% EtOAc in hexane) to yield the title compound as an off-white solid (40.3 mg, 59%). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) \(t_R = 8\) min (enantiomer 1), 14 min (enantiomer 2). Flow rate 0.75 mL min\(^{-1}\).

The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (41.8 mg, 61% yield, 99:1 e.r.).

\textbf{mp:} 132-134 °C.

\textbf{\(^1\text{H NMR (500 MHz, CDCl}_3\):} \(\delta\) 5.97 (s, 1H), 5.86 (dt, \(J = 6.9, 1.5\) Hz, 1H), 4.04 (s, 1H), 3.36 (dd, \(J = 6.9, 2.4\) Hz, 1H), 3.23 (dd, \(J = 8.6, 2.0\) Hz, 1H), 3.16 (t, \(J = 1.9\) Hz, 1H), 3.12 (dd, \(J = 8.7, 1.9\) Hz, 1H), 2.49 (hept, \(J = 7.4\) Hz, 1H), 2.32 (s, 1H), 1.91 – 1.80 (m, 1H), 1.25 (s, 3H), 1.23 (s, 3H), 1.14 (d, \(J = 7.0\) Hz, 3H), 1.12 (s, 3H), 0.90 (d, \(J = 6.7\) Hz, 3H), 0.86 (d, \(J = 6.9\) Hz, 3H).

\textbf{\(^{13}\text{C NMR (126 MHz, CDCl}_3\):} 212.45, 202.10, 166.66, 145.86, 126.27, 120.16, 73.64, 73.11, 56.01, 44.80, 42.24, 41.10, 33.45, 33.07, 32.44, 26.05, 23.13, 20.92, 20.25, 19.42.

\textbf{LCMS (ESI\(^+\)):} \(m/z\) calcd. for \(\text{C}_{20}\text{H}_{29}\text{O}_4\) 333.2; found 333.1 [M+H].

\([\alpha]_D^{25} = + 50.9^\circ\) (c = 0.11, CHCl\(_3\)).
The enantioselective reaction was achieved according to general procedure F, using catalyst \textit{ent-6a}. The crude mixture was purified by flash column chromatography (hexanes-EtOAc), to obtain the product as a white solid (45.6 mg, 66% yield, 97.5:2.5 e.r.). Analytical data was identical to that described for (+)-biscarvacrol.
3,10-Dihydroxy-6,12-dimethoxy-3,10-dimethyltricyclo[6.2.2.0^2,7]dodeca-5,11-diene-4,9-dione\(^{15}\) (3j)

The racemic material was prepared using general procedure E from 2-methyl-5-methoxyphenol (0.41 mmol). Preparative TLC (1:1 CH\(_2\)Cl\(_2\):EtOAc) was performed on the crude reaction mixture after thermolysis at 70 °C for 1 h, in order to obtain a racemic sample. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) \(t_R = 15\) min (enantiomer 1), 35 min (enantiomer 2). Flow rate 0.75 mL min\(^{-1}\)

The enantioselective reaction was achieved according to a modified version of general procedure F, in which the tertiary amine catalyst 8 was employed (10 mol%). Conversion of the SM was confirmed by TLC (3:1 hexane:EtOAc). LCMS analysis could identify the major product as the non-dimerized o-quinol, and so the neat crude reaction mixture was heated to 70 °C for 1 h.\(^{15}\) The desired product could then be identified by LCMS, and the crude mixture was subsequently purified by flash column chromatography (CH\(_2\)Cl\(_2\)-EtOAc)* to afford the product as a white solid (33.4 mg, 53% yield, 98:2 e.r.).

*other chromatography eluents were found to contaminate the product with residual iminium catalyst.

**mp:** 209-211 °C (decomp.)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.43 (s, 1H), 4.84 (dd, \(J = 7.5, 2.4\) Hz, 1H), 4.11 (s, 1H), 3.69 (s, 3H), 3.43 (s, 3H), 3.36 (dd, \(J = 7.5, 2.0\) Hz, 1H), 3.33 (t, \(J = 2.6\) Hz, 1H), 3.25 (dd, \(J = 8.8, 2.7\) Hz, 1H), 3.16 (dd, \(J = 8.8, 2.0\) Hz, 1H), 1.33 (s, 3H), 1.30 (s, 3H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 209.99, 200.39, 172.31, 154.61, 100.15, 99.85, 72.69, 72.11, 56.56, 56.30, 55.34, 43.53, 42.39, 40.56, 32.60, 25.72.

LCMS (ESI\(^+\)): \(m/z\) calcd. for C\(_{16}\)H\(_{21}\)O\(_6\) 309.1 found 309.0 [M+H].
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

5,8-di-tert-butyl-3,10-dihydroxy-3,10-dimethyltricyclo[6.2.2.0²,⁷]dodeca-5,11-diene-4,9-dione (3I)

The racemic material was prepared using general procedure E from 2-tert-butyl-6-methyl-phenol (0.41 mmol). Prep. TLC was performed on the crude product using 1:1 hexanes:EtOAc to obtain a racemic sample of the title compound. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) t_R = 7.5 min (enantiomer 1), 23 min (enantiomer 2). Flow rate 0.75 mL min⁻¹. The enantioselective reaction was achieved according to general procedure F. The crude mixture was purified by flash column chromatography (hexane-EtOAc), to obtain the product as a pale yellow solid (37 mg, 50% yield, 92.5:7.5 e.r.).

mp: 109-111 °C.
IR (cm⁻¹): 3521, 3445, 2964, 2963, 1713, 1684.
¹H NMR (500 MHz, CDCl₃): δ 6.35 – 6.29 (m, 2H), 5.92 (dd, J = 8.7, 0.7 Hz, 1H), 4.20 (br s, 1H), 3.34 (dt, J = 6.9, 1.6 Hz, 1H), 3.24 (ddd, J = 8.3, 5.3, 0.7 Hz, 1H), 3.04 (dd, J = 8.3, 1.8 Hz, 1H), 2.61 (br s, 1H), 1.26 – 0.97 (m, 24H).
¹³C NMR (126 MHz, CDCl₃): 217.41, 203.81, 145.83, 135.91, 135.64, 129.64, 74.86, 74.65, 63.36, 43.90, 43.23, 42.85, 35.07, 33.57, 31.21, 29.24, 28.70, 25.10.
HRMS (ESI⁺): m/z calcd. for C₂₂O₄H₂₂Na 383.2193; found 383.2191 [M+Na].
Dearomatization of 2-methyl-6-benzylphenol

![Chemical structure](image)

The racemic material was prepared using general procedure E from 2-methyl-6-benzylphenol (0.41 mmol). The mixture of bicyclo[2.2.2]octenone products was isolated by column chromatography (0 → 60% EtOAc in hexane). Preparative TLC was then performed (9:1 CH₂Cl₂/EtOAc) to separate the two products in order to obtain HPLC samples. Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA), flow rate 0.75 mL min⁻¹.

Product **3m**: \( t_R = 12.5 \text{ min} \) (enantiomer 1), 15.0 min (enantiomer 2).

Product **3n**: \( t_R = 14.0 \text{ min} \) (enantiomer 1), 16.0 min (enantiomer 2).

The enantioselective reaction was achieved according to general procedure F, where the crude mixture was purified by flash column chromatography (hexanes:EtOAc) to obtain a mixture of the two products as a white solid (69.9 mg, 80% yield, 1:1 isomeric ratio). The two products were then separated by a further chromatographic purification (0 → 5% EtOAc in CH₂Cl₂). The characterisation of hetero-dimer **3m** was in agreement with literature.¹⁶
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

(3R)-5,10-dibenzyl-3,10-dihydroxy-3,8-dimethyltricyclo[6.2.2.0^2,7]dodeca-5,11-diene-4,9-dione\(^1\) (3m)

\[
\text{mp: } 130-132 \, ^\circ\text{C.}
\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.34 – 7.26 (m, 4H), 7.24 – 7.18 (m, 1H), 7.17 – 7.10 (m, 4H), 6.33 (dd, \(J = 8.0, 6.8\) Hz, 1H), 6.13 (d, \(J = 4.4\) Hz, 1H), 5.54 (dd, \(J = 8.1, 1.2\) Hz, 1H), 3.85 (s, 1H), 3.58 (d, \(J = 15.3\) Hz, 1H), 3.52 (d, \(J = 15.3\) Hz, 2H), 3.22 (dt, \(J = 6.7, 1.7\) Hz, 1H), 3.12 (dd, \(J = 8.3, 1.9\) Hz, 1H), 2.88 (dd, \(J = 8.3, 4.5\) Hz, 1H), 2.78 (d, \(J = 14.0\) Hz, 1H), 2.72 (d, \(J = 13.9\) Hz, 1H), 2.25 (s, 1H), 1.27 (s, 3H), 1.13 (s, 3H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 213.58, 202.20, 140.03, 138.45, 135.30, 135.00, 133.50, 132.87, 129.08, 128.69, 128.59, 127.30, 126.71, 75.25, 73.82, 54.19, 44.80, 43.33, 42.93, 42.03, 36.42, 31.41, 15.79.

LCMS (ESI\(^+\)): \(m/z\) calcd. for C\(_{28}\)H\(_{29}\)O\(_4\) 429.2 found 429.1 [M+H].
(3R)-3,10-dibenzyl-3,10-dihydroxy-5,8-dimethyltricyclo[6.2.2.0^{2,7}]dodeca-5,11-diene-4,9-dione (3n)

**mp:** 67-69 °C

**IR (cm⁻¹):** 3455, 2923, 2852, 1722, 1680.

**¹H NMR (400 MHz, CDCl₃):** δ 7.33 – 7.25 (m, 3H), 7.18 – 7.13 (m, 5H), 6.98 – 6.94 (m, 2H), 6.36 (dd, J = 4.2, 1.4 Hz, 1H), 6.31 (dd, J = 8.0, 6.8 Hz, 1H), 5.58 (dd, J = 8.1, 1.1 Hz, 1H), 3.87 (s, 1H), 3.29 (dd, J = 8.2, 1.8 Hz, 1H), 3.24 (dt, J = 6.8, 1.7 Hz, 1H), 3.03 – 2.98 (m, 1H), 2.93 – 2.83 (m, 2H), 2.81 – 2.70 (m, 2H), 2.28 (s, 1H), 1.74 (t, J = 1.5 Hz, 3H), 1.42 (s, 3H).

**¹³C NMR (126 MHz, CDCl₃):** δ 213.88, 201.51, 139.18, 136.79, 135.32, 135.30, 135.02, 133.61, 130.51, 129.95, 128.60, 128.21, 127.32, 127.16, 77.40, 75.46, 54.26, 50.72, 45.23, 43.35, 42.57, 41.94, 16.38, 15.94.

**HRMS (ESI⁺):** m/z calcd. for C_{28}H_{38}O_{4} 451.1880; found 451.1880 [M+Na].
Synthesis of ent-bis(2,6-xylenol) using Amine pre-catalyst 8

The reaction was carried out in an identical manner to general procedure F, employing amine 8 instead of 6a. To a stirred mixture of the phenol (0.41 mmol), amine 8 (10 mol%), and Na₂CO₃ (2.46 mmol) in 1:1 MeCN-H₂O (2.5 mL) at 0 °C, H₂O₂ (126 μL, 30% aq. soln) was added. The resulting mixture was then stirred overnight at 0 °C, before quenching with Na₂S₂O₃. The reaction was then diluted with CH₂Cl₂ and extracted with CH₂Cl₂ (2 x 15 mL). The combined organics were then dried over MgSO₄, filtered, and concentrated in vacuo. Purification was achieved using flash column chromatography (0 → 80% EtOAc in hexane) to afford the product as a white solid (43 mg, 75% yield, 95:5 e.r.). Spectral data was identical to that when using general procedure E or F.
Gram Scale Synthesis of ent-bis(2,6-xylenol) with reduced loading

Na₂CO₃ (6.5 g, 61.3 mmol) was added to a stirred solution of 2,6-dimethylphenol (1.5 g, 12.3 mmol), and the amine pre-catalyst 8 (148 mg, 0.31 mmol) in 1:1 MeCN-H₂O (75 mL). The resulting suspension was cooled to 0 °C, before adding H₂O₂ (3.78 mL, 30% aq. solution) dropwise, over approximately 15 minutes. The reaction mixture was then stirred rapidly overnight at 0 °C, before quenching with Na₂S₂O₅. MeCN was then removed in vacuo, before extracting with CH₂Cl₂ (3 x 100 mL). The combined organics were then dried over MgSO₄, filtered, and concentrated to afford the crude product. Purification was achieved using flash column chromatography (0 → 50% EtOAc in hexane), to afford the product as a white solid (1.1 g, 65%, 92.5:7.5 e.r.). Spectral data was identical to that reported from the standard procedure.

Figure S5. Set-up of the gram-scale dearomatization.
Retro-[4+2]/[4+2] reactions of ent-bis(2,6-xylenol)

6-(4-chlorophenyl)-3-hydroxy-1,3-dimethylbicyclo[2.2.2]octa-5,7-dien-2-one (9)

ent-bis(2,6-xylenol) (30 mg, 0.11 mmol, 92.5:7.5 e.r.), 4-chlorophenyl acetylene (218 mg, 1.6 mmol) and dry toluene (2 mL) were added to a microwave vial at room temperature (20 °C). The mixture was then purged with argon, before placing in the microwave reactor. The reaction mixture was irradiated for a total of 4 h, maintaining a temperature of 140 °C. The reaction was then cooled, before removing toluene in vacuo. Purification was then achieved using flash column chromatography (0 → 60% EtOAc in hexane) to afford the product as a colourless oil (59 mg, 98% yield, 92:8 e.r.). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) t_R = 6.8 min (enantiomer 1), 7.6 min (enantiomer 2). Flow rate 0.75 mL min⁻¹.

IR (cm⁻¹): 3461, 2975, 2933, 1721.

¹H NMR (400 MHz, CDCl₃): δ 7.29 – 7.22 (m, 2H), 7.02 – 6.97 (m, 2H), 6.61 – 6.53 (m, 1H), 6.44 (d, J = 6.2 Hz, 1H), 6.16 (dd, J = 7.2, 1.9 Hz, 1H), 3.83 (td, J = 6.3, 1.9 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 206.37, 144.20, 135.90, 135.72, 135.45, 134.06, 133.61, 129.99, 128.32, 69.60, 58.51, 48.44, 27.07, 14.58.

HRMS (ESI⁺): m/z calcd. for C₁₆H₁₅ClO₂Na 295.1305; found 295.1304 [M+Na].
1-hydroxy-1,3,6,7-tetramethyl-1,2,4a,5,8,8a-hexahydropyrenal-2-one (10)

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{OHMe} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\(130^\circ C\) toluene

\(\mu W\)

\(\text{ent-bis}(2,6\text{-xylenol})\) (30 mg, 0.11 mmol, 92.5 : 7.5 e.r.), 1,3-dimethyl butadiene (0.18 mL, 1.6 mmol) and dry toluene (2 mL) were added to a microwave vial at room temperature (20 °C). The mixture was then purged with argon, before placing in the microwave reactor. The reaction mixture was irradiated for a total of 4 h, maintaining a temperature of 130 °C. The reaction was then cooled, before removing toluene in vacuo. Purification was then achieved using flash column chromatography (0 → 40% EtOAc in hexane) to afford the product as a colourless oil (45 mg, 93%, 91:9 e.r.). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) \(t_R= 8.5\ \text{min} \) (enantiomer 1), 13 min (enantiomer 2). Flow rate 0.75 mL min\(^{-1}\).

**IR (cm\(^{-1}\)):** 3498, 2975, 2920, 2894, 1671.

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** \(\delta 6.36 – 6.33\) (m, 1H), 3.61 (s, 1H), 3.00 – 2.85 (m, 1H), 2.48 – 2.37 (m, 1H), 2.34 – 2.24 (m, 1H), 2.08 (dd, \(J = 18.0, 6.7\ \text{Hz}\), 1H), 1.97 (d, \(J = 17.3\ \text{Hz}\), 1H), 1.79 (dd, \(J = 2.7, 1.4\ \text{Hz}, 3H\)), 1.63 (s, 3H), 1.53 (s, 3H), 1.36 (s, 3H).

**\(^{13}\)C NMR (101 MHz, CDCl\(_3\)):** \(\delta 203.49, 150.77, 132.53, 125.55, 123.75, 77.07, 43.94, 37.60, 33.95, 28.84, 24.52, 19.13, 19.08, 15.75.

**HRMS (ESI\(^+\)):** m/z calcd. for C\(_{14}\)H\(_{20}\)O\(_2\)Na 243.1356; found 243.1356 [M+Na].
3-hydroxy-7-(4-methoxyphenyl)-1,3-dimethylbicyclo[2.2.2]oct-5-en-2-one (11)

**Ent-bis(2,6-xylenol)** (30 mg, 0.11 mmol, 92.5 : 7.5 e.r.), 4-methoxy styrene (0.14 mL, 1.10 mmol) and dry toluene (2 mL) were added to a microwave vial at room temperature (20 °C). The mixture was then purged with argon, before placing in the microwave reactor. The reaction mixture was irradiated for 1 h, maintaining a temperature of 130 °C. The reaction was then cooled, before removing toluene in *vacuo*. Purification was then achieved using flash column chromatography (0 → 40% EtOAc in hexane) to afford the product as a white solid, in quantitative yield (ca. 10:1 regiomeric ratio of inseparable isomers, 91.5:8.5 e.r.). Chiral HPLC was achieved with Chiralpak IC column (75:25 Hexane:IPA) *t*R = 7.6 min (enantiomer 1), 9 min (enantiomer 2). Flow rate 0.75 mL min⁻¹.

**mp:** 117 °C.

**IR (cm⁻¹):** 3426, 2962, 2930, 1721, 1612.

**¹H NMR (400 MHz, CDCl₃):** δ 7.08 – 7.02 (m, 2H), 6.81 – 6.75 (m, 2H), 6.63 (dd, *J* = 8.1, 6.9 Hz, 1H), 5.80 – 5.76 (m, 1H), 3.78 (s, 3H), 3.01 – 2.95 (m, 1H), 2.94 – 2.78 (m, 2H), 2.46 (s, 1H), 1.64 – 1.54 (m, 1H), 1.32 (s, 3H), 0.89 (s, 3H).

**¹³C NMR (101 MHz, CDCl₃):** δ 214.16, 158.61, 136.66, 135.38, 131.63, 129.78, 113.66, 72.31, 55.36, 53.06, 43.78, 32.30, 26.32, 15.88.

**HRMS (ESI⁺):** *m/z* calcd. for C₁₇H₂₀O₃Na 295.1305; found 295.1304 [M+Na].
Unsuccessful substrates

- Low yielding para-dearomatization
- No conversion
- Messy/complex mixture
- Messy/complex mixture
- Messy/complex mixture
- Undesired, unidentified product
Mechanistic Studies

i) Direct HRMS observation of the oxaziridinium ion

Na$_2$CO$_3$ (1 mg) followed by Oxone (6 mg) was added to a solution of Binapthylazepinium catalyst 6a (2 mg) in 1:1 CH$_2$Cl$_2$-H$_2$O (1 mL), at room temperature (20 °C). The solution was vigorously mixed for around 30 seconds, and then the two layers were allowed to partition. A sample was then taken from the organic layer, diluted with MeOH, and immediately analysed by ESI-HRMS. This allowed for the observation of m/z=500.2220, which corresponds to the oxaziridinium ion 12. Isotopic patterns agreed well with the predicted spectrum.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

Figure S6. Direct HRMS analysis of oxidant + catalyst mixture, (a) iminium ion (b) zoomed in view of the spectrum to show oxaziridinium 12 (b). Both species show predicted m/z values as well as isotopologue patterns.

ii) Stoichiometric dearomatization reaction using an isolated oxaziridinium salt

3,4-Dihydroisoquinoline\(^{17}\) (S12)

\[
\text{NBS (1.47 g, 8.3 mmol), was added to 1,2,3,4-tetrahydroisoquinoline (0.94 mL, 7.5 mmol) in CH}_2\text{Cl}_2\text{ (40 mL), at } 0 \text{ °C. The resulting solution was then allowed to warm to room temperature (20 °C), and stirred for a further 1 h. 30% NaOH (10 mL) was then added, and the resulting mixture was stirred for 1 h. The organic layer was then separated, before acidifying with 10% HCl (2 x 20 mL). The acidic aqueous extracts were then basified using aqueous NH}_3\text{, before extracting with CH}_2\text{Cl}_2\text{ (3 x 30 mL). The combined organic extracts were then dried over MgSO}_4\text{, filtered, and concentrated in vacuo. Purification of the crude product was achieved by flash column chromatography (100% EtOAc) to afford the title compound as a pale-yellow oil (752 mg, 76%).}
\]

\(^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 8.31 (t, J = 2.2 Hz, 1H), 7.32 (td, J = 7.2, 1.9 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.12 (dd, J = 7.3, 0.4 Hz, 1H), 3.74 (ddd, J = 8.0, 6.3, 2.2 Hz, 2H), 2.75 – 2.68 (m, 2H).\)

\(^13\text{C NMR (101 MHz, CDCl}_3\text{): } \delta 160.39, 136.40, 131.10, 128.59, 127.48, 127.25, 127.14, 47.47, 25.10.\)

LCMS (ESI\(^+\)): m/z calcd. for C\(_{9}\)H\(_9\)N 132.1; found 132.0 [M+H].
3,4-dihydroisoquinoline 1,2-oxide\(^{18}\) (S13)

![Chemical structure of 3,4-dihydroisoquinoline 1,2-oxide](image)

To a stirred solution of 3,4-dihydroisoquinoline (650 mg, 5.0 mmol) in MeOH-CH\(_2\)Cl\(_2\) (5:1 v/v, 120 mL), m-CPBA (1.34 g, ~70%, 5.4 mmol) was slowly added at 0 °C. NaHCO\(_3\) (416 mg, 5.0 mmol) was then added, before allowing the reaction mixture to warm to room temperature (20 °C). The reaction was stirred at r.t. for 20 h, before diluting with CH\(_2\)Cl\(_2\) (50 mL). The organics were washed with sat. Na\(_2\)SO\(_3\) solution (2 x 30 mL), followed by sat. NaHCO\(_3\) (30 mL), and finally with brine (30 mL). The organic layer was then separated, dried over MgSO\(_4\), filtered, and concentrated in vacuo. The crude product was then purified by flash column chromatography (100% EtOAc) to afford the oxaziridine as a pale-yellow oil (252 mg, 35%).

\(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.51 (dd, \(J = 7.4, 1.2\) Hz, 1H), 7.36 (td, \(J = 7.5, 1.4\) Hz, 1H), 7.30 (t, \(J = 7.4\) Hz, 1H), 7.13 (d, \(J = 7.4\) Hz, 1H), 4.94 (s, 1H), 3.93 – 3.82 (m, 1H), 2.95 – 2.80 (m, 2H), 2.54 – 2.44 (m, 1H).

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) 135.38, 130.13, 129.88, 129.24, 127.97, 126.78, 74.44, 48.77, 23.82.

\(\text{LCMS (ESI+) } m/z\) calcd. for C\(_9\)H\(_9\)N\(_2\)O: 148.1; found 148.0 [M+H].

2-Methyl-4,8b-dihydro-3H-oxazireno[3,2-a]isoquinolin-2-ium tetrafluoroborate\(^{19}\) (14)

![Chemical structure of 2-Methyl-4,8b-dihydro-3H-oxazireno[3,2-a]isoquinolin-2-ium tetrafluoroborate](image)

To a stirred solution of oxaziridine S13 (92.5 mg, 0.63 mmol) in dry CH\(_2\)Cl\(_2\) (5 mL), MeOTf (0.11 mL, 0.97 mmol) was added dropwise, at 0 °C. The reaction was then stirred at 0 °C for a further 30 min, before warming to room temperature (20 °C). NaBF\(_4\) (75 mg, 0.68 mmol), in the minimum volume of acetone, was then slowly added, before stirring at r.t. for 15 min. Solvents were then removed in vacuo, and the resulting solid was triturated in Et\(_2\)O, to afford the oxaziridinium salt as an off-white solid (127 mg, 81%). The oxaziridinium salt was found to partially decompose into the corresponding iminium salt (~18% by \(^1\text{H NMR}\)), which can be identified by both LC-MS and \(^1\text{H NMR}\).

\(^{1}\text{H NMR}\) (400 MHz, CD\(_3\)CN): \(\delta\) 7.83 (d, \(J = 7.6\) Hz, 1H), 7.64 (t, \(J = 7.6\) Hz, 1H), 7.50 (t, \(J = 7.4\) Hz, 1H), 7.38 (d, \(J = 7.6\) Hz, 1H), 6.19 (s, 1H), 4.35 (dd, \(J = 13.3, 6.2\) Hz, 1H), 4.35 (dd, \(J = 13.3, 6.2\) Hz, 1H), 3.88 (tt, \(J = 10.0, 5.0\) Hz, 1H), 3.76 (s, 3H), 3.15 (ddd, \(J = 18.6, 12.5, 6.2\) Hz, 1H), 3.02 (dd, \(J = 16.9, 4.7\) Hz, 1H).

\(^{13}\text{C NMR}\) (101 MHz, CD\(_3\)CN): \(\delta\) 134.64, 134.31, 133.29, 129.91, 129.08, 122.61, 84.95, 54.19, 51.15, 24.96.

\(\text{LCMS (ESI+)}\): \(m/z\) calcd. for C\(_{10}\)H\(_{12}\)NO\(_+\): 162.1; found 162.0 [M\(^+\)].
Stoichiometric dearomatization using 14 to form 3a

To a stirred solution of 2,6-dimethylphenol (45 mg, 0.34 mmol) and Na₂CO₃ (109 mg, 1.03 mmol) in H₂O (1.25 mL), a solution of freshly prepared oxaziridinium tetrafluoroborate 14 (115 mg, ~82%, 0.38 mmol) in MeCN (1.25 mL) was added dropwise, at 0 °C. The reaction was then warmed to r.t., and stirred for 20 h. The reaction was then quenched with Na₂S₂O₃, before diluting with CH₂Cl₂ (10 mL), and extracting with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were then dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then purified by automated flash column chromatography (0 → 80% EtOAc) to afford 3a as a white solid (17.5 mg, 37% yield, 70% brsm). Analytical data was identical to that reported from general procedure E or F.
X-ray Crystallography

The crystal structures of 3a and 3g were solved and refined routinely and further details are presented in Tables S3 – S6 and in the deposited cif files. CCDC 2152267 & 2152268 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

For 3a: This is a redetermination of the structure published in the CSD with REFCODE: EHMNAP10. That structure, determined in 1973, had an $R$ factor of 6.6% and was measured at room temperature. This re-determination is of significantly superior quality with an $R$ factor of 3.3% and was measured at 100 K.

Figure S7. Displacement ellipsoid plot of 3a at the 50% probability level showing an intramolecular S(5) H-bond.

Figure S8. Hydrogen bonded centro-symmetric dimer pairs in the crystal structure of 3a with S(5) and $R^2_2(10)$ graph set motifs. Most H atoms omitted for clarity.
**Table S3**

Experimental details for 3a

| Crystal data |  |
|--------------|---|
| Chemical formula | C_{16}H_{20}O_{4} |
| \( M_{r} \) | 276.32 |
| Crystal system, space group | Monoclinic, \( P2_{1}/n \) |
| Temperature (K) | 100 |
| \( a, b, c \) (Å) | 8.36115 (6), 11.87163 (7), 14.50532 (11) |
| \( \beta \) (°) | 104.3438 (7) |
| \( V \) (Å³) | 1394.92 (2) |
| \( Z \) | 4 |
| Radiation type | Cu Kα |
| \( \mu \) (mm⁻¹) | 0.77 |
| Crystal size (mm³) | 0.36 × 0.28 × 0.12 |

**Data collection**

| Diffractometer | Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 goniometer and HyPix 6000 detector |
|----------------|-----------------------------------------------------------------|
| Absorption correction | Multi-scan CrysAlis PRO 1.171.41.105a (Rigaku Oxford Diffraction, 2021). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. |

\( T_{\text{min}}, T_{\text{max}} \) | 0.881, 1.000 |

No. of measured, independent and observed \([I > 2\sigma(I)]\) reflections | 18199, 2495, 2469 |

\( R_{\text{int}} \) | 0.014 |

\((\sin \theta/\lambda)_{\text{max}}\) (Å⁻¹) | 0.602 |

**Refinement**

| \( R(F^2 > 2\sigma(F^2)), wR(F^2), S \) | 0.033, 0.077, 1.03 |
| No. of reflections | 2495 |
| No. of parameters | 261 |
| H-atom treatment | All H-atom parameters refined |
| \( \Delta\alpha_{\text{max}}, \Delta\alpha_{\text{min}} \) (e Å⁻³) | 0.28, -0.17 |

Computer programs: CrysAlis PRO 1.171.41.105a (Rigaku OD, 2021), SHELXT-2018/2 (Sheldrick, 2015), SHELXL2018/3 (Sheldrick, 2018), Bruker SHELXTL.
Table S4

Hydrogen-bond geometry (Å, °) for (3a)

|       | D—H   | H···A  | D···A  | D—H···A |
|-------|-------|-------|-------|---------|
| O1—H1—O2 | 0.82 (3) | 2.23 (3) | 2.6621 (13) | 114 (2) |
| C6—H6—O3 | 0.976 (13) | 2.279 (13) | 2.7915 (13) | 111.7 (9) |
| O3—H3—O4i | 0.889 (19) | 1.912 (19) | 2.7838 (11) | 166.3 (16) |

Symmetry code: (i) -x+1, -y, -z+1.

Figure S9. Displacement ellipsoid plot of 3g at the 50% probability level showing an intramolecular S(5) H-bond. Most H atoms omitted for clarity.
Figure S10. H-bonded, C(7) zig-zag chains and S(5) motifs in the crystal structure of 3g. Most H atoms omitted for clarity.

For 3g: The key point is that the absolute structure was reliably determined.

Table S5
Experimental details for 3g

| Crystal data         |                      |
|----------------------|----------------------|
| Chemical formula     | C₃₀H₇₀F₂O₄           |
| Mᵣ                  | 492.54               |
| Crystal system, space group | Monoclinic, P2₁ |
| Temperature (K)      | 100                  |
| a, b, c (Å)          | 11.67041 (19), 8.92920 (13), 12.4767 (2) |
| β (°)                | 108.8488 (18)        |
| V (Å³)               | 1230.44 (4)          |
| Z                    | 2                    |
| Radiation type       | Cu Kα                |
| μ (mm⁻¹)             | 0.80                 |
| Crystal size (mm³)   | 0.17 × 0.09 × 0.03   |
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

Data collection

| Diffractometer                          | Rigaku 007HF equipped with Varimax confocal mirrors and an AFC11 quarter χ goniometer and HyPix 6000 detector |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------|
| Absorption correction                  | Analytical. CrysAlis PRO 1.171.41.122a (Rigaku Oxford Diffraction, 2021) Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived by R.C. Clark & J.S. Reid. (Clark, R. C. & Reid, J. S. (1995). Acta Cryst. A51, 887-897) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. |

| $T_{\text{min}}$, $T_{\text{max}}$          | 0.955, 0.990 |
| No. of measured, independent and observed [$I > 2\sigma(I)$] reflections | 52195, 4624, 4415 |
| $R_{\text{int}}$                           | 0.036 |
| ($\sin \theta/\lambda_{\text{max}}$ (Å$^{-1}$) | 0.612 |

Refinement

| $R(F^2 > 2\sigma(F^2))$, $wR(F^2)$, $S$ | 0.027, 0.071, 1.06 |
| No. of reflections                      | 4624 |
| No. of parameters                       | 337 |
| No. of restraints                       | 1 |
| H-atom treatment                        | H atoms treated by a mixture of independent and constrained refinement |
| $\Delta_f^{\text{max}}$, $\Delta_f^{\text{min}}$ (e Å$^{-3}$) | 0.12, -0.12 |
| Absolute structure                      | Flack x determined using 1952 quotients [(I+)-(I-)]/[(I+)+(I-)] (Parsons, Flack and Wagner, Acta Cryst. B69 (2013) 249-259). |
| Absolute structure parameter            | -0.02 (6) |

Computer programs: CrysAlis PRO 1.171.41.122a (Rigaku OD, 2021), SHELXT-2018/2 (Sheldrick, 2015), SHELXL2018/3 (Sheldrick, 2018), Bruker SHELXTL.

Table S6

Hydrogen-bond geometry (Å, °) for (3g)

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|-------------|-------|--------|----------|------------|
| O3—H3···O1i | 0.88 (3) | 1.98 (3) | 2.7954 (19) | 153 (3) |
| O1—H1···O2  | 0.84 (3) | 2.04 (3) | 2.5877 (18) | 122 (3) |
| C13—H13B···O4ii | 0.99 | 2.57 | 3.476 (2) | 151 |
| C18—H18···F2iii | 0.95 | 2.58 | 3.402 (3) | 145 |
| C27—H27···F1iv | 0.95 | 2.57 | 3.429 (3) | 151 |

Symmetry codes: (i) -x, y+1/2, -z+1; (ii) -x, y-1/2, -z+1; (iii) -x+1, y+1/2, -z+1.
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
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![Chemical Structure](image)

![NMR Spectrum](image)
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
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Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

(~5.5:1 oxaziridinium : iminium)

(~5.5:1 oxaziridinium : iminium)
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
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Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
key NOE enhancements

![Chemical structure diagram]

**1H spectrum**

- NOE 3.1 ppm
- NOE 6.25 ppm
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

\[ \text{\textsuperscript{1}H COSY} \]

\[ \text{TDO-4718_2} \]

\[ \text{gradient absolute value cosy} \]

\[ \text{HMOC} \]

\[ \text{TDO-4718_2} \]
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

HMBC

TOD-471b_2
gradient enhanced HMBC

\[ \text{HMBC} \]
key NOE enhancements

$\text{H spectrum}$

$\text{NOE 5.9 ppm}$

$\text{H spectrum}$
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

![Chemical Structure Image]
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

key NOE enhancements

!

'H spectrum

NOE 5.9 ppm

NOE 3.0 ppm
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
key NOE enhancements

$^1$H spectrum

NOE 5.9 ppm

$^1$H spectrum
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
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Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

1H COSY

HMOC
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
key NOE enhancements

[Chemical Structure Image]

1H spectrum

NOE 6.3 ppm

NOE 3.3 ppm
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization

key NOE enhancements

H spectrum

1H spectrum

NOE 6.34 ppm

NOE 6.28 ppm

NOE 5.90 ppm

NOE 3.02 ppm
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
key NOE enhancements

[diagram]

$^1$H spectrum

NOE 5.75 ppm

NOE 6.62 ppm

$^1$H spectrum

$^1$H spectrum

NOE 0.87 ppm

$^1$H spectrum
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylative Phenol Dearomatization
key NOE enhancements

**1H spectrum**

NOE 6.33 ppm

NOE 1.33 ppm

NOE 2.28 ppm

**1H spectrum**
Organocatalytic Enantioselective Synthesis of Bicyclo[2.2.2]octenones via Oxaziridinium Catalyzed ortho-
Hydroxylative Phenol Dearomatization
Organocatalytic Enantioselective Synthesis of Bicyco[2.2.2]octenones via Oxaziridinium Catalyzed ortho-Hydroxylicative Phenol Dearomatization

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