Supporting Information

for

Catalytic asymmetric formal synthesis of beraprost

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1. General information
All reactions were carried out under a positive atmosphere of argon in dried glassware. Analytical thin-layer chromatography was performed with Silica gel 60 (Merck). Column chromatography was performed on Merck silica gel 60 (230–400 mesh) or Fuji Silysia silica gel (NH, 100–200 mesh), and flash column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Proton nuclear magnetic resonance (1H NMR) spectra were recorded on a JEOL JNM-ECA 500 at 500 MHz, and AL400 at 400 MHz. Chemical shifts are reported relative to Me₄Si (δ 0.00) in CDCl₃. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (13C NMR) spectra were recorded on a JEOL JNM-ECA 500 at 126 MHz, and AL400 at 100 MHz. Chemical shifts are reported relative to Me₄Si (δ 0.00) in CDCl₃ and internal residual solvent (MeOD-d₄ δ 3.31). Infrared spectra were recorded on a FT/IR-4100 Fourier-transform infrared spectrometer ATR (attenuated total reflectance). High-resolution mass spectra were obtained on a Shimazu LCMS-IT-TOF fitted with an ESI. Optical rotations were determined with a JASCO P-2200KDT polarimeter and are the average of five measurements. All melting points were measured on Büchi M-565 melting point apparatus and are uncorrected.

2. Experimental details

**Preparation of catalyst**

![Chemical structure](image)

3-(1H-Imidazol-1-yl)-6-(trifluoromethyl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (S2)

A solution of 2-amino-4-(trifluoromethyl)benzenesulfonamide [1] (S1, 2.97 g, 12.4 mmol) and N,N'-thiocarbonyldiimidazole (4.40 g, 24.7 mmol) in dioxane (50 mL) was refluxed for 5 h. The solvent was removed by distillation under reduced pressure, and the residue was suspended in water (50 mL). A solution of NaOH in water (2.0 g/20 mL) was added, and the solution was stirred at room temperature for 20 min. The alkaline solution was treated with 6 N HCl (40 mL). The precipitate was collected by filtration, washed with water, and dried to give the pale yellow solid of S2 (3.07 g, 78%).

Mp: 180 °C (decomposed); 1H NMR (500 MHz, CDCl₃): δ 9.74 (s, 1H), 8.22 (s, 1H), 7.93 (d, J=8.6 Hz, 1H), 7.75 (s, 1H), 7.57–7.58 (m, 2H) ppm, two N–H protons could not be observed; 13C NMR (101 MHz, CDCl₃): δ 147.2, 145.2, 134.8, 131.9 (q, J = 31.8 Hz), 127.3, 124.3, 123.6 (q, J = 273 Hz), 122.1 (d, J = 4.8 Hz), 120.3 (q, J = 3.8 Hz), 119.3, 118.7 ppm; IR (Zn/Se-ATR) 3537, 3150, 1590, 1545, 1428, 1334 cm⁻¹; HRMS (ESI⁺) Cacld. for C₁₁H₈N₄O₂F₃S ([M+H]⁺): 317.0315, found: 317.0329.
3-(((1R,2R)-2-(Dimethylamino)cyclohexyl)amino)-6-(trifluoromethyl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (Catalyst E)

The mixture of S2 (318.3 mg, 1.0 mmol) and (R, R)-N,N,N′,N′-dimethyl-trans-diaminocyclohexane [2] (213.4 mg, 1.5 mmol) was stirred at 150 °C for 6 h. The reaction mixture was dissolved in CHCl₃ (20 mL) and was washed with saturated aqueous NH₄Cl solution (10 mL) and saturated aqueous NaHCO₃ (10 mL). The organic layer dried over anhydrous Na₂SO₄. The solvent was evaporated and the resulting crude residue purified by column chromatography on silica gel (NH) eluting with chloroform/methanol (9/1) to afford E (128.6 mg, 33%) as brown amorphous.

1H NMR (400 MHz, CDCl₃): δ 8.03 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.4 Hz, 1H), 7.07 (s, 1H), 3.45 (brs, 1H), 2.60–2.48 (m, 8H), 2.24 (brs, 1H), 2.00–1.98 (m, 1H), 1.89–1.87 (m, 1H), 1.80–1.77 (m, 1H), 1.32–1.23 (m, 5H), ppm; 13C NMR (101 MHz, CDCl₃): δ 152.6, 137.8, 134.1 (q, J = 32.6 Hz), 125.2, 124.7, 123.0 (q, J = 273 Hz), 120.0 (d, J = 3.8 Hz), 114.6, 67.6, 52.8, 40.2, 32.8, 29.7, 24.4, 22.2 ppm; IR (Zn/Se-ATR) 3304, 2939, 1633, 1125 cm⁻¹; HRMS (ESI⁺) Calcd. for C₁₆H₂₂N₂O₂F₃S ([M+H]⁺): 391.1410: found: 391.1391.

Catalytic asymmetric synthesis of important intermediate 2

(E)-4-(3-Bromo-2-hydroxyphenyl)-N-methoxy-N-methylbut-2-enamide (7)

To the solution of o-bromophenol (9, 9.84 g, 56.9 mmol) and K₂CO₃ (15.3 g, 111 mmol) in acetone (125 mL) was added allyl bromide (10 g, 82.2 mmol), and the reaction mixture was refluxed at 70 °C for 2 h. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The resulting mixture was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to give the crude allyl ether, which was used for the next reaction without further purification.

The crude ether (11.0 g) was dissolved in hexane (130 mL), and Et₂AlCl (1.0 M in hexane, 53 mL, 53 mmol) was added at room temperature. After being stirred at the same temperature for 3.5 h, the reaction mixture was cooled to 0 °C and quenched by careful addition of 2N HCl (35 mL). The aqueous phase was then separated and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 2-allyl-6-bromophenol (11, 12.7 g), which was directly subject to the next ozonolysis. A crude solution of 11 in MeOH (150 mL) was cooled to −78 °C, and O₃ gas was bubbled through the solution at −78 °C until the starting material had disappeared. The reaction was quenched with Me₂S (5.6 mL, 75.7 mmol), slowly warmed to room temperature before the addition of water (60 mL). The resulting mixture was stirred for 1 h and concentrated under reduced
pressure. The residue was diluted with EtOAc and washed with water. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give the crude aldehyde as a mixture with the corresponding lactol, which seemed to be unstable on silica gel [3].

Then, the resulting crude (12, 9.66 g) was immediately dissolved in THF (150 mL) and N-Methoxy-N-methyl(triphenylphosphoranylidene)acetamide (13, 18.2 g, 50 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 1.5 hours. After concentration, the residue was directly purified by column chromatography on silica gel (n-hexane/EtOAc = 3/1) to afford 7 as white solid (9.8 g, 55% in 4 steps).

White solid; M.p.103–105 °C; ∆H NMR (500 MHz, CDCl₃): δ 7.35 (dd, J = 8.0, 1.4 Hz, 1H), 7.11 (t, J = 7.0 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.76 (t, J = 7.9 Hz, 1H), 6.44 (d, J = 15.2 Hz, 1H), 5.63 (s,1H), 3.68 (s, 3H), 3.61 (dd, J = 6.9, 1.4 Hz, 2H), 3.23 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 166.7, 150.1, 144.3, 130.3, 129.7, 126.2, 121.5, 120.0, 110.6, 61.8, 33.5, 32.2 ppm; IR (Zn/Se ATR) 3154, 1657, 1612, 1448 cm⁻¹; HRMS (ESI⁺) Cacl. for C₁₂H₁₃BrNO₃ ([M+H]⁺): 300.0230, found: 300.0216; Elemental analysis Cacl. for C₁₂H₁₃BrNO₃: C, 48.02; H, 4.70; N, 4.67; found: C, 47.83; H,4.67; N:4.73.

![8](image)

(E)-4-(2-Hydroxy-3-methylphenyl)-N-methoxy-N-methylbut-2-enamide (8)

A solution of 2-allyl-6-methylphenol (10, 2.01 g, 13.6 mmol) in MeOH (50 mL) was cooled to −78 °C. O₃ gas was bubbled through the solution at −78 °C until the starting material had disappeared. The reaction was quenched with Me₂S (1.1 mL, 14.8 mmol), slowly warmed to room temperature before the addition of water (20 mL). The resulting mixture was stirred for 1 h and concentrated under reduced pressure. The residue was diluted with EtOAc and washed with water. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give the crude aldehyde, which was similarly, as described above, treated with 13 (4.94 g, 13.6 mmol) in THF (50 mL). The reaction mixture was stirred for 1.5 hours. After concentration, the residue was directly purified by column chromatography on silica gel (n-hexane/EtOAc = 3/1) to afford 8 as pale yellow solid (1.53 g, 48% in 2 steps).

Pale yellow solid; M.p.101.8–103.7 °C; ∆H NMR (500 MHz, CDCl₃): δ 7.14 (dt, J₁ = 15.3 Hz, J₂ = 6.7 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 6.43 (d, J = 15.2 Hz, 1H), 4.88 (s, 1H), 3.66 (s, 3H), 3.57 (dd, J₁ = 6.9 Hz, J₂ = 1.4 Hz, 2H), 3.26 (s, 3H), 2.25 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 166.9, 152.3, 145.9, 129.4, 128.1, 124.4, 123.9, 120.3, 119.3, 61.7, 33.7, 32.4, 16.1 ppm; IR (Zn/Se ATR) 3394, 3008, 2977, 2932, 2885, 1653, 1614, 1469, 1196 cm⁻¹; HRMS (ESI⁺) Cacl. for C₁₃H₁₇NNaO₃ ([M+Na]⁺): 258.1101, found: 258.1090.
General procedure for asymmetric intramolecular oxa-Michael reaction (5, 6)

To a solution of 7 or 8 (1.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added catalyst A–E (1–10 mol %), and the resulting mixture was stirred for the indicated time in Table 1. The reaction mixture was then evaporated and the resulting crude residue was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (2/1) to afford 5 or 6.

(R)-2-(7-Bromo-2,3-dihydrobenzofuran-2-yl)-N-methoxy-N-methylacetamide (5)

White solid; Mp 51–52 °C; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.24 (d, $J = 8.0$ Hz, 1H), 7.08 (d, $J = 7.4$ Hz, 1H), 6.71 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 5.31–5.25 (m, 1H), 3.69 (s, 3H), 3.56 (dd, $J_1 = 15.9$ Hz, $J_2 = 9.0$ Hz, 1H), 3.20 (m, 4H), 3.06 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.2$ Hz, 1H), 2.78 (dd, $J_1 = 16.0$ Hz, $J_2 = 8.0$ Hz, 1H) ppm; $^{13}$C NMR (126 MHz, CDCl$_3$): δ 170.9, 156.6, 131.2, 128.3, 124.2, 121.9, 102.6, 80.2, 61.6, 38.4, 36.7, 32.1 ppm; IR (Zn/Se-ATR) 1650, 1453 cm$^{-1}$; HRMS (ESI$^+$) Cacl. for C$_{12}$H$_{15}$BrNO$_3$ ([M+H]$^+$): 300.0230, found: 300.0206; HPLC [CHIRALPAK IB, n-hexane/2-propanol = 95/5, 1.0 mL/min, $\lambda = 220$ nm, retention times: (minor) 10.3 min (major) 12.1 min; $[\alpha]^{26}_{D} +43.6$ (c 0.83, CHCl$_3$) for 86% ee.

(R)-N-Methoxy-N-methyl-2-(7-methyl-2,3-dihydrobenzofuran-2-yl)acetamide (6)

Colorless oil; $^1$H NMR (400 MHz, CDCl$_3$): δ 6.99 (d, $J = 7.3$ Hz, 1H), 6.92 (d, $J = 7.3$ Hz, 1H), 6.74 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 5.23–5.19 (m, 1H), 3.67 (s, 3H), 3.45 (dd, $J_1 = 15.6$ Hz, $J_2 = 9.2$ Hz, 1H), 3.21 (s, 3H), 3.13 (dd, $J_1 = 15.8$ Hz, $J_2 = 5.7$ Hz, 1H), 2.94 (dd, $J_1 = 15.6$ Hz, $J_2 = 6.9$ Hz, 1H), 2.71 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.3$ Hz, 1H), 2.19 (s, 3H) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): δ 171.2, 157.4, 129.1, 125.6, 122.3, 120.2, 119.4, 78.8, 61.2, 38.3, 35.9, 31.8, 15.2 ppm; IR (Zn/Se-ATR) 2939, 1660, 1466, 1439, 1193 cm$^{-1}$; HRMS (ESI$^+$) Cacl. for C$_{13}$H$_{18}$NO$_3$ ([M+H]$^+$): 236.1281, found: 236.1284; HPLC [CHIRALPAK IB, n-hexane/2-propanol = 95/5, 1.0 mL/min, $\lambda = 238$ nm, retention times: (minor) 8.5 min (major) 7.8 min; $[\alpha]^{26}_{D} +3.88$ (c 1.48, CHCl$_3$) for 91% ee.
**tert-Butyl (R)-2-diazo-4-(7-methyl-2,3-dihydrobenzofuran-2-yl)-3-oxobutanoate (14)**

To a solution of LHMDS (16.2 mL, 16.2 mmol, 1.0 M solution in THF) in dry THF (16 mL) was added t-BuOAc (1.88 g, 16.2 mmol) at −40 ºC dropwise over 10 min under argon atmosphere, and the reaction mixture was stirred at the same temperature for 30 min order to generate lithium enolate. To the reaction mixture was added THF solution (16.0 mL) of 6 (1.15 g, 5.37 mmol) dropwise over 15 min, and the reaction mixture was stirred at the same temperature until TLC indicated the reaction was complete (30 min). The reaction was quenched with saturated aqueous NH₄Cl solution, and the product was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to furnish the crude β-ketoester (1.88 g), which was dissolved in THF (40 mL) and CH₃CN (10 mL). To this solution were added 2-azido-1,3-dimethylimidazolium hexafluorophosphate (ADMP; 2.30 g, 8.06 mmol) and K₂HPO₄ (1.87 g, 10.75 mmol) successively at 0 ºC, and the reaction mixture was stirred for 2 h, before being quenched with saturated aqueous NH₄Cl solution (15 mL) and water (15 mL). The organic layers were extracted with CHCl₃ three times. The combined extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc = 10/1) to afford 14 including an inseparable impurity 24 (1.51 g; 14/24 = 10/1) as yellow oil.

^1H NMR (400 MHz, CDCl₃, 14/24 = 10:1); product 14, δ 6.98 (d, J = 7.2 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.73 (dd, J₁ = 6.6 Hz, 1H), 5.28–5.19 (m, 1H), 3.49 (dd, J₁ = 16.4 Hz, J₂ = 6.4 Hz, 1H), 3.43 (dd, J₁ = 16.0 Hz, J₂ = 6.8 Hz, 1H), 3.11 (dd, J₁ = 16.8 Hz, J₂ = 6.8 Hz, 1H), 2.90 (dd, J₁ = 16.0 Hz, J₂ = 6.4 Hz, 1H) 2.17 (s, 3H), 1.51 (s, 9H); signals of 24: 2.44 (s, 3H), 1.53 (s, 9H) ppm; ^13C NMR (101 MHz, CDCl₃): product 14, δ 190.0, 160.2, 157.5, 129.1, 125.4, 122.2, 120.2, 119.6, 83.3, 78.1, 77.2, 46.3, 35.9, 28.1, 15.1; signal of 24: 28.2 ppm; HRMS (ESI⁺) Calcd. for C₁₁H₂₀N₂O₄ ([M+Na]⁺): 339.1315, found: 339.1313.

**tert-Butyl (1R, 2R, 3aS, 8bS)-2-hydroxy-5-methyl-2,3,3a,8b-tetrahydro-1H-cyclopenta-β-benzofuran-1-carboxylate (15)**

To a crude of 14 (758.0 mg, 2.40 mmol) in CH₂Cl₂ (20 mL) was added Rh₂(OAc)₄ (10.6 mg, 1.0 mol %), and the resulting mixture was stirred at ambient temperature for 15 min, when TLC indicated the reaction...
was complete. MeOH (10 mL) was then added, and NaBH₄ (271.9 mg, 7.19 mmol) was added portionwise –40 °C. The mixture was stirred at –40 °C for 2 h and at the ambient temperature for additional 2 h, before being quenched with saturated aqueous NH₄Cl solution (20 mL). The organic materials were extracted with EtOAc three times, and the combined organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, and evaporated to give the crude residue, which was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (7/1) to afford 15 (490.0 mg, 60% in 4 steps from 6) as white solid; Mp.73.2–73.4 °C; ¹H NMR (500 MHz, CDCl₃): δ 7.12 (d, J = 7.2 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.79 (dd, J₁ = J₂ = 7.4 Hz, 1H), 5.17 (dd, J₁ = 9.0 Hz, J₂ = 7.2 Hz, J₃ = 5.2 Hz, 1H), 4.38–4.33 (m, 1H), 3.92 (t, J = 8.0 Hz, 1H), 2.79 (t, J = 7.0 Hz, 1H), 2.59 (ddd, J₁ = 13.4 Hz, J₂ = J₃ = 6.7 Hz, 1H), 2.39 (dd, J₁ = 4.7 Hz, J₂ = 3.0 Hz, 1H), 2.20 (s, 3H), 2.07 (ddd, J₁ = 13.4 Hz, J₂ = 8.0 Hz, J₃ = 5.3 Hz, 1H), 1.53 (s, 9H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ 172.7, 157.3, 129.9, 129.0, 122.2, 120.7, 120.0, 84.8, 81.8, 74.6, 60.3, 48.0, 41.1, 28.2, 15.3 ppm; IR (Zn/Se-ATR) 3466, 2978, 2872, 1699 cm⁻¹; HRMS (ESI⁺) Cacl. for C₁₇H₂₂NaO₄ [(M+Na)+]: 313.1410, Found: 313.1398; [α]⁺二十五 +80.2 (c 0.79, CHCl₃).

Acetal 16

To a solution of 15 (513.5 mg, 1.77 mmol) in Et₂O (17 mL) was added LiBH₄ (115.6 mg, 5.31 mol), and the resulting mixture was stirred at ambient temperature for 9 h. The reaction was quenched with 1 N aqueous HCl solution (10 mL), and the organic materials were extracted with EtOAc three times. The combined extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and evaporated to afford the crude diol (367.9 mg), which was then dissolved in THF (16 mL). To this solution were added 1,1-diethoxyethane (2.5 mL, 17.6 mmol) and p-TsOH·H₂O (31.8 mg, 10 mol%), and the reaction mixture was stirred at 60 °C for 3 h before being quenched with saturated aqueous NaHCO₃ solution (15 mL). The mixture was extracted with EtOAc three times, and the combined extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and evaporated to give the crude acetal, which was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (15/1) to afford 16 (292.6 mg, 71% in 2 steps from 15) as white solid; Mp.125.5–129.0 °C; ¹H NMR (500 MHz, CDCl₃): δ 6.97 (d, J = 7.4 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.75 (dd, J₁ = J₂ = 7.4 Hz, 1H), 5.10 (q, J = 7.5 Hz, 1H), 4.72 (q, J = 5.0 Hz, 1H), 4.39 (dd, J₁ = 10.5 Hz, J₂ = 4.2 Hz, 1H), 3.71 (ddd, J₁ = J₂ = 10.5 Hz, 1H), 3.41 (td, J₁ = 11.0, J₂ = 6.3 Hz, 1H), 3.15 (t, J = 10.0 Hz, 1H), 2.74 (ddd, J₁ = 12.8 Hz, J₂ = J₃ = 6.4 Hz, 1H), 2.20 (s, 3H), 1.97 (td, J₁ = 12.1 Hz, J₂ = 5.9 Hz, 1H), 1.88 (ddd, J₁ = 21.6 Hz, J₂ = 10.7 Hz, J₃ = 4.2 Hz, 1H), 1.36 (d, J = 5.2 Hz, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ 157.5, 129.8, 128.0, 121.3, 120.3, 120.1, 99.5, 83.4, 79.6, 70.8, 48.1, 45.3, 37.9, 20.6, 15.3 ppm; IR (Zn/Se-ATR) 2952, 1464, 1384 cm⁻¹; [α]⁺二十五 +7.5 (c 0.4, CHCl₃).
**Bromide 17**

To the solution of 16 (40.0 mg, 0.162 mmol) and NBS (34.7 mg, 0.195 mmol) in CCl₄ (2.5 mL) was added azobisisobutyronitrile (AIBN, 3.2 mg, 0.0195 mmol) at room temperature, and the mixture was heated under reflux for 3 h. The crude mixture was filtered through a pad of Celite, and the filtrate was concentrated to give the crude, which was then purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (10/1) to afford 17 (7.4 mg, 14%) as yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 7.17 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.82 (dd, J₁ = J₂ = 7.5 Hz, 1H), 5.23–5.19 (m, 1H), 4.73 (q, J = 5.0 Hz, 1H), 4.53 (d, J = 10.0 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 4.40 (dd, J₁ = 10.0 Hz, J₂ = 5.0 Hz, 1H), 3.73 (t, J₁ = 11.0 Hz, 1H), 3.44 (td, J₁ = J₂ = 11.0 Hz, J₂ = 6.5 Hz, 1H), 3.18 (dd, J₁ = 11.0 Hz, J₂ = 9.0 Hz, 1H), 2.78 (ddd, J₁ = 12.5 Hz, J₂ = J₃ = 6.5 Hz, 1H), 2.01 (td, J₁ = 12.2 Hz, J₂ = 5.8 Hz, 1H), 1.85 (ddd, J₁ = 21.7 Hz, J₂ = 10.8 Hz, J₃ = 4.4 Hz, 1H), 1.36 (d, J = 5.2 Hz, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ 157.3, 129.6, 129.5, 124.5, 120.9, 99.6, 84.5, 79.5, 70.7, 48.2, 45.1, 37.8, 28.0, 20.6 ppm; IR (Zn/Se-ATR) 2986, 2938, 2856, 1728, 1599, 1455 cm⁻¹; [α]²⁶D +40.6 (c 1.15, CHCl₃).

![Diagram of compound 17](image)

**tert-Butyl (R)-4-(7-bromo-2,3-dihydrobenzofuran-2-yl)-3-oxobutanoate (19)**

To a solution of LiHMDS (1.2 mL, 1.2 mmol, 1.0 M solution in THF) in dry THF (1.2 mL) was added t-BuOAc (139.4 mg, 1.2 mmol) at −40 °C dropwise over 10 min under argon atmosphere, and the reaction mixture was stirred at the same temperature for 30 min. To the reaction mixture was added AlBr₃ (324.9 mg, 1.22 mmol) in THF (3.6 mL) dropwise over 10 min, and stirred at the same temperature for 20 min, before the subsequent dropwise addition of amide 5 (120.1 mg, 0.40 mmol) in THF (1.0 mL) over 15 min. The reaction mixture was stirred at the same temperatures until TLC indicated the reaction was complete (2 h), and then quenched with saturated aqueous NH₄Cl solution. The product was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (n-hexane/EtOAc = 10/1) to afford 28 (128.1 mg, 90%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃, keto/enol = 11:1); keto form, δ 7.26 (d, J = 6.3 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.73 (dd, J₁ = J₂ = 7.7 Hz, 1H), 5.24 (dt, J₁ = 15.0 Hz, J₂ = 7.5 Hz, 1H), 3.56 (ddd, J₁ = 15.9 Hz, J₂ = 9.0 Hz, 1H), 3.44 (s, 2H), 3.24 (dd, J₁ = 17.2 Hz, J₂ = 5.4 Hz, 1H), 2.97 (dd, J₁ = 16.9 Hz, J₂ = 7.4 Hz, 2H), 1.47 (s, 9H); selected signals for enol form: 5.19–5.13 (m, 1H), 5.00 (s, 1H), 3.10 (dd, J₁ = 15.8 Hz, J₂ = 6.6 Hz, 1H), 2.83 (dd, J₁ = 14.0 Hz, J₂ = 6.0 Hz,
1H), 2.48 (dd, \( J_1 = 14.2 \) Hz, \( J_2 = 8.2 \) Hz, 1H), 1.50 (s, 9H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 200.6, 166.0, 156.3, 131.2, 127.7, 123.9, 122.0, 102.6, 82.3, 78.9, 51.0, 48.5, 36.4, 27.9 ppm; IR (Zn/Se-ATR) 2979, 1733, 1713. 1454 cm\(^{-1}\); HRMS (ESI\(^+\)) Cacld. for C\(_{16}\)H\(_{19}\)NaO\(_4\)Br ([M+Na\(^+\]): 377.0359, found: 377.0346; \([\alpha]\)\(^D\) +5.2 (c 1.85, CHCl\(_3\)).

tert-Butyl (\(R\))-4-(7-bromo-2,3-dihydrobenzofuran-2-yl)-2-diazo-3-oxobutanoate (20)

To a mixture of ketoester 19 (825.2 mg, 2.32 mmol) and 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP; 794.8 mg, 2.79 mmol) in THF/CH\(_3\)CN (16 mL/4.0 mL) was added K\(_2\)HPO\(_4\) (809.3 mg, 4.65 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH\(_4\)Cl solution (10 mL) and additional water (8 mL). The organic materials were extracted with CHCl\(_3\) three times, and the combined extracts were washed with brine (20 mL), dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduce pressure to afford the crude diazoester 20, which was then purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (8/1) to afford white solid. This solid was recrystallized with hexane/Et\(_2\)O (1:1), and the enantioenriched product 20 was obtained from filtrate (376.6 mg, 43%, 95% ee). White solid; Mp. 88.6–92.9 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.24 (d, \( J = 8.2 \) Hz, 1H), 7.07 (d, \( J = 8.2 \) Hz, 1H), 6.71 (dd, \( J_1 = J_2 = 7.8 \) Hz, 1H), 5.36–5.29 (m, 1H), 3.57–3.51 (m, 2H), 3.17 (dd, \( J_1 = 17.2 \) Hz, \( J_2 = 7.1 \) Hz, 1H), 3.00 (dd, \( J_1 = 15.8 \) Hz, \( J_2 = 7.1 \) Hz, 1H), 1.52 (s, 9H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 189.7, 160.3, 156.5, 131.1, 127.8, 123.9, 121.8, 102.7, 83.5, 79.3, 77.2, 46.0, 36.5, 28.3 ppm; IR (Zn/Se-ATR) 2130, 1710, 1643 cm\(^{-1}\); HRMS (ESI\(^+\)) Cacld. for C\(_{16}\)H\(_{17}\)N\(_2\)NaO\(_4\) ([M+Na\(^+\]): 403.0269, Found: 403.0264; HPLC [Chiralpak IB, \( n\)-hexane/2-propanol = 99/1, 1.0 mL/min, \( \lambda = 254 \) nm, retention times: (major) 16.7 min (minor) 10.1 min]; \([\alpha]\)\(^D\) +24.3 (c 0.86, CHCl\(_3\)) for 95% ee.

tert-Butyl (\(1R\),\(2R\),\(3aS\),\(8bS\))-5-bromo-2-hydroxy-2,3,\(3a\),\(8b\)-tetrahydro-1H-cyclopenta-\(\beta\)-benzofuran-1-carboxylate (21)

To a solution of 20 (376.0 mg, 0.986 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added Rh\(_2\)(OAc)\(_4\) (4.4 mg, 1.0 mol%), and the resulting mixture was stirred at ambient temperature for 15 min, when TLC indicated the reaction was complete. MeOH (5.0 mL) was added, and NaBH\(_4\) (111.9 mg, 2.96 mmol) was added portionwise at –40 °C. The mixture was stirred for 4 h before being quenched with saturated aqueous NH\(_4\)Cl solution (10
The organic materials were extracted with EtOAc three times, and the combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduce pressure to afford the crude residue, which was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (6/1) to afford 21 (235.0 mg, 67% in 2 steps from 20) as white solid. Mp.109.0–112.0 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.30 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 7.0 Hz, 1H), 6.76 (dd, J₁ = J₂ = 7.8 Hz, 1H), 5.29–5.24 (m, 1H), 4.38 (dd, J₁ = 13.9 Hz, J₂ = 7.0 Hz, 1H), 4.02 (dd, J₁ = J₂ = 8.1 Hz, 1H), 2.80 (dd, J₁ = J₂ = 7.0 Hz, 1H), 2.38 (ddd, J₁ = 13.8 Hz, J₂ = J₃ = 7.0 Hz, 1H), 2.33 (brs, 1H), 2.14 (ddd, J₁ = 13.9 Hz, J₂ = 8.1 Hz, J₃ = 5.2 Hz, 1H), 2.33 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.2, 156.3, 131.8, 131.2, 123.8, 122.1, 102.7, 85.7, 82.0, 74.4, 48.5, 41.0, 28.1 ppm; IR (Zn/Se-ATR) 3477, 2982, 2899, 1696, 1459 cm⁻¹; HRMS (ESI⁺) Calcd. for C₁₆H₁₂BrNaO₄ ([M⁺Na⁺]: 377.0359, Found: 377.0366; HPLC [Chiralpak OJ3, n-hexane/2-propanol = 95/5, 1.0 mL/min, λ = 254 nm, retention times: (major) 11.7 min (minor) 14.9 min]; [α] D²⁶ +82.7 (c 0.70, CHCl₃).

Acetal (22)

To a solution of 21 (467.7 mg, 1.32 mmol) in Et₂O (10 mL) was added LiBH₄ (86.03 mg, 3.95 mol), and the resulting mixture was stirred at ambient temperature for 15 h. The reaction was quenched with 1 N aqueous HCl solution (20 mL), and the organic materials were extracted with EtOAc three times. The combined extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford the crude diol, which was then dissolved in THF (10 mL). To this solution, were added 1,1-diethoxyethane (1.5 mL, 10.5 mmol) and p-TsOH·H₂O (25.2 mg, 10 mol %), and the reaction mixture was stirred at 60 °C for 3 h, before being quenched with saturated aqueous NaHCO₃ solution (10 mL). The product was extracted with EtOAc three times, and the combined extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and evaporated to give the resulting crude residue, which was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (8/1) to afford 22 (283.2 mg, 69% in 2 steps from 21) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.31 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.74 (dd, J₁ = J₂ = 7.6 Hz, 1H), 5.22 (td, J₁ = 7.9 Hz, J₂ = 7.5 Hz, 1H), 4.73 (q, J = 5.0 Hz, 1H), 4.39 (dd, J₁ = 10.5 Hz, J₂ = 4.6 Hz, 1H), 3.73 (dd, J₁ = J₂ = 10.5 Hz, 1H), 3.42 (td, J₁ = 11.2, J₂ = 6.1 Hz, 1H), 3.26 (dd, J₁ = 11.0 Hz, J₂ = 9.2 Hz, 1H), 2.78 (ddd, J₁ = 13.0 Hz, J₂ = J₃ = 6.5 Hz, 1H), 2.06 (td, J₁ = 12.1 Hz, J₂ = 6.0 Hz, 1H), 1.88 (ddd, J₁ = 12.9 Hz, J₂ = 7.5 Hz, J₃ = 5.2 Hz, 1H), 1.36 (d, J = 5.0 Hz, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ 156.4, 131.8, 130.2, 123.0, 122.0, 102.9, 99.6, 84.4, 79.4, 70.6, 48.1, 46.0, 37.7, 20.6 ppm; IR (Zn/Se-ATR) 2990, 1451, 1388 cm⁻¹; HRMS (ESI⁺) Calcd. for C₁₂H₁₃NaO₃Br ([M-C₂H₃+Na⁺]): 306.9940, Found: 306.9925; [α] D²⁶ +43.0 (c 0.98, CHCl₃).
Ester 23

To a solution of the acetal 22 (76.7 mg, 0.246 mmol) in THF (2.5 mL) was added TMEDA (0.04 mL 0.32 mmol) at −78 °C, and the reaction mixture was stirred for 10 minutes. To this solution was added a n-hexane solution of n-BuLi (1.55 M, 0.2 mL, 0.3 mmol) at −78 °C, and the mixture stirred at the same temperature for 5 minutes before the subsequent dropwise addition of 3-formylpropionate (85.7 mg, 0.738 mmol) in THF (1.0 mL) over 5 minutes. The reaction mixture was stirred at −78 °C for 30 min, and quenched with saturated aqueous NH₄Cl solution (3.0 mL). The organic materials were extracted with EtOAc three times, and the combined extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to give crude ester. The residue was purified by column chromatography on silica gel eluting with n-hexane/ethyl acetate (2/1) to afford 23 (49.8 mg, 58%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.15 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.74 (t, J = 7.3 Hz, 1H), 5.16 (q, J = 7.2 Hz, 1H), 4.80 (q, J = 6.0 Hz, 1H), 4.73 (q, J = 4.9 Hz, 1H), 4.39 (dd, J₁ = 10.5 Hz, J₂ = 4.1 Hz, 1H), 3.73 (t, J = 10.8 Hz, 1H), 3.67 (s, 3H), 3.43 (td, J₁ = 11.2, J₂ = 6.4 Hz, 1H), 3.16 (t, J = 9.8 Hz, 1H), 2.78–2.70 (m, 2H), 2.45 (q, J = 6.8 Hz, 2H), 2.11 (ddd, J₁ = 13.6 Hz, J₂ = J₃ = 6.8 Hz, 1H), 1.96 (td, J₁ = 12.1 Hz, J₂ = 5.8 Hz, 1H), 1.82 (qd, J₁ = 10.8 Hz, J₂ = 4.1 Hz, 1H), 1.69 (d, J = 6.8 Hz, 1H), 1.36 (d, J = 4.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 174.3, 155.7, 129.0, 126.2, 125.9, 123.1, 120.9, 99.6, 84.3, 79.5, 70.7, 70.2, 51.6, 48.2, 44.8, 37.9, 32.1, 30.4, 20.6 ppm; IR (Zn/Se-ATR) 3461, 2949, 1732, 1450 cm⁻¹; HRMS (ESI⁺) Cacl. for C_{19}H_{24}NaO₆ ([M+Na]⁺): 371.1465, Found: 371.1477; [α]²⁶_D +31.4 (c 0.67, CHCl₃).

Methyl 4-((1S,2R,3aS,8bS)-2-Hydroxy-1-(hydroxymethyl)-2,3,3a,8b-tetrahydro-1H-cyclopenta-β-benzofuran-5-yl)butanoate (2) [4]

To the solution of 23 (103.5 mg 0.297 mmol) in wet MeOH (5.0 mL) was added pyridinium p-toluenesulfonate (PPTS, 630.0 mg 2.51 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The organic materials were extracted with EtOAc three times, and the combined extracts were washed with brine (5 mL), dried over anhydrous Na₂SO₄, and evaporated to give the crude diol, which was then dissolved in CH₂Cl₂ (4.0 mL). To this solution were added Et₃SiH (0.5 mL, 3.13
mmol) and TFA (0.1 mL 1.35 mmol) at 0 °C dropwise, and the reaction mixture was stirred at 0 °C for 1.5 h, before being quenched with saturated aqueous NaHCO₃ solution (3.0 mL). The organic materials were extracted with EtOAc three times, and the combined extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford crude 2, which was then purified by preparative thin layer chromatography on silica gel with n-hexane/ethyl acetate (1/4) as eluent to afford key intermediate 2 (33.7 mg 37% in 2 steps from 23) as white solid. Mp. 51.6–55.6 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.02 (d, J = 7.3 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.79 (t, J = 7.3 Hz, 1H), 5.13 (ddd, J₁ = 8.8 Hz, J₂ = 7.2 Hz, J₃ = 4.8 Hz, 1H), 4.13 (q, J = 6.9 Hz, 1H), 3.97 (dd, J₁ = 10.3 Hz, J₂ = 5.3 Hz, 1H), 3.79 (t, J = 9.2 Hz, 1H), 3.65 (s, 3H), 3.42 (t, J = 8.0 Hz, 1H), 2.55–2.65 (m, 3H), 2.32 (t, J = 7.3 Hz, 2H), 2.17 (ddd, J₁ = 13.4 Hz, J₂ = J₃ = 6.7 Hz, 1H), 2.05 (ddd, J₁ = 13.2 Hz, J₂ = 8.0 Hz, J₃ = 5.2 Hz, 1H), 1.90–2.01 (m, 2H), 1.58–1.62 (brs, 2H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 174.2, 157.1, 130.2, 128.9, 123.4, 122.0, 120.7, 85.4, 75.9, 64.9, 56.8, 51.5, 47.5, 41.9, 33.4, 29.2, 24.8 ppm; IR (Zn/Se-ATR) 3383, 2929, 1728, 1453 cm⁻¹; HRMS (ESI⁺) Calcd. for C₁₇H₂₂NaO₅ ([M+Na]⁺): 329.1359, Found: 329.1367; HPLC [Chiralpak AD, n-hexane/2-propanol = 95/5, 1.0 mL/min, λ = 238 nm, retention times: (major) 42.8 min (minor) 38.3 min]; [α]ᵢ²⁶ +12.5 (c 1.25, CHCl₃) for 95% ee.

3. Reference
(1) Deping, C.; Kevin, D. J.; Duke, F. M.; Antony, S. N.; Rosanna, T.; Kenneth, W. J.; Michael, Z. N. Eur. Pat. Appl. W52313, 2004.
(2) Mitchell, J. M.; Finney, N. S. Tetrahedron Lett. 2000, 41, 8431.
(3) Hintermann, L.; Ackerstaff, J.; Boeck, F. Chem. Eur. J. 2013, 19, 2311
(4) Reddy, N. K.; Vijaykumar, B. V. D.; Chandrasekhar, S. Org. Lett. 2012, 14, 299.
4. Copies of $^1$H and $^{13}$C NMR charts
5. Copies of HPLC charts

--- Shimadzu LCsolution Analysis Report ---

Sample ID: 10
Method Name: 1.0-95-auto-shoki10-4-4.lcm
Acquisition Date: 2013/05/01 11:46:30
Modified Date: 2013/06/29 18:47:31

Chromatogram:

--- Shimadzu LCsolution Analysis Report ---

Sample ID: 136(10)
Method Name: 95-IPA5-4.4-auto-shoki-30min.lcm
Acquisition Date: 2013/12/04 20:16:06
Modified Date: 2013/12/04 21:58:40

Chromatogram:
Shimadzu LCsolution Analysis Report

Sample ID: C:\data_131217\Kuramoto\#201-300\#275-IB-1.0-95.lcd
Method name: rac=methyl
Acquisition date: 2014/05/27 16:57:48
Modified date: 2014/05/28 11:52:55

Chromatogram

Peak Report
Peak table: C:\data_131217\Kuramoto\#201-300\#275-IB-1.0-95.lcd

Shimadzu LCsolution Analysis Report

Sample ID: C:\data_131217\Kuramoto\#301-400\#315-IB-0.7-99.lcd
Method name: 27595-I\PA5-4.4-auto-shoki-20min.lcm
Acquisition date: 2014/07/10 22:30:58
Modified date: 2015/09/12 10:38:46

Chromatogram

Peak Report
Peak table: C:\data_131217\Kuramoto\#301-400\#315-IB-0.7-99.lcd

S32
Shimadzu LCsolution Analysis Report

sample ID: 266p(115)
method name: 99-IPA, 1.0-4.4-10min-1.0v-auto.lcm
acquisition date: 2014/05/22 15:19:07
modified date: 2014/05/28 16:43:50

<Chromatogram>

peak table C:\data_131217\Kuramoto\201-300\266p(115)-IB-1.0-99.lcd

| peak # | retention time (min) | area  | area (%) |
|--------|---------------------|-------|----------|
| 1      | 10.709              | 189238| 3.462    |
| 2      | 16.366              | 5276934| 96.538  |
Shimadzu LC solution Analysis Report

Sample ID: C:\data_131217\Kuramoto\201-300\244-AD-1.0-95.lcd
Method name: rac-formal
Acquisition date: 2014/04/25 16:28:57
Modified date: 2015/09/11 22:12:50

Chromatogram:

Peak Report:

| Peak # | Retention time (min) | Area | Area (%) |
|--------|----------------------|------|----------|
| 1      | 38.286               | 183781 | 47.956   |
| 2      | 42.831               | 199445 | 52.044   |

Shimadzu LC solution Analysis Report

Sample ID: C:\data_131217\Kuramoto\201-300\297(244)-AD-1.0-95.lcd
Method name: (244):IPA-5-2.2-auto-shoki-60min.lcm
Acquisition date: 2014/07/10 18:24:18
Modified date: 2015/09/11 21:32:56

Chromatogram:

Peak Report:

| Peak # | Retention time (min) | Area | Area (%) |
|--------|----------------------|------|----------|
| 1      | 42.656               | 32899 | 2.555    |
| 2      | 47.775               | 1246956 | 97.445  |
6. Computational details

The proposed transition states for oxa-Michael reactions (B3LYP/6-31G* level using Gaussian 09)
The energy profile of the reaction pathway estimated by DFT calculations at B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* level using Gaussian 09.)
Cartesian coordinates and total energies for all the calculated structures

**Substrate 8**

Zero-point vibrational energy: 740289.1 (Joules/Mol)  
176.93334 (Kcal/Mol)

| Zero-point correction= 0.281961 (Hartree/Particle) |
|-----------------------------------------|
| Thermal correction to Energy= 0.300108 |
| Thermal correction to Enthalpy= 0.301053 |
| Thermal correction to Gibbs Free Energy= 0.233570 |
| Sum of electronic and zero-point Energies= -785.685771 |
| Sum of electronic and thermal Energies= -785.667624 |
| Sum of electronic and thermal Enthalpies= -785.666680 |
| Sum of electronic and thermal Free Energies= -785.734162 |

\[ E(RB3LYP) = -785.967732157 \]
\[ E(RB3LYP/6-311+G**) = -786.196320217 \]

| 0 1 |
|-----|
| C   | 0.30861700  |
| C   | 1.34822000  |
| C   | 2.54184200  |
| O   | 2.72128300  |
| C   | -0.94736500 |
| C   | -2.17699300 |
| C   | -4.41157600 |
| C   | -2.47917300 |
| C   | -3.01945300 |
| C   | -4.13232200 |
| C   | -3.59706200 |
| O   | -1.63484400 |
| N   | 3.51742200  |
| C   | 3.23669100  |
| O   | 4.56105200  |
| C   | 5.57976400  |
| C   | -3.89643600 |
| H   | -3.08016400 |
| H   | -4.07399700 |
| H   | -4.79564300 |

S37
H        4.11501300  2.34088100  0.93236500
H        2.38891600  1.96856700  1.12487200
H        3.01090200  2.49874900 -0.45733300
H        5.96963900 -0.28088200  0.53381000
H        6.36963800 -0.28088200 -1.12487200
H        5.20511700 -1.43564800 -0.49466000
H        1.32681600  0.29986500  1.59690000
H       -0.84168700 -0.59076900  2.24310800
H       -1.08698700 -2.27255500  1.75419300
H       -2.79648600 -2.88194800  0.18236800
H       -5.27789600  0.17315700 -1.39732000
H       -4.77727700 -2.32395000 -1.17048200
H        0.36398600 -1.88903100 -0.30436000
H       -1.95029400  2.30135700  0.70211200

Product 6
Zero-point vibrational energy    746086.3 (Joules/Mol)
                                   178.31891 (Kcal/Mol)
Zero-point correction=           0.284169 (Hartree/Particle)
Thermal correction to Energy=    0.301237
Thermal correction to Enthalpy=  0.302181
Thermal correction to Gibbs Free Energy=  0.237638
Sum of electronic and zero-point Energies=   -785.708093
Sum of electronic and thermal Energies=      -785.691026
Sum of electronic and thermal Enthalpies=    -785.690081
Sum of electronic and thermal Free Energies= -785.754624
E(RB3LYP) =  -785.992262589
E(RB3LYP/6-311+G**) =  -786.209488474

0 1
C         0.12912900  0.16896500  0.64672500
C        -1.09240500  0.81013000 -0.00151000
C        -2.37169800  0.05882200  0.36467100
O         -2.37474200 -0.87244000  1.15715100
C         0.53213800 -1.22472100  0.10042700
C         2.02687400 -1.07603100 -0.06564600
| Atom | X Position  | Y Position  | Z Position  |
|------|-------------|-------------|-------------|
| C    | 4.63442700  | -0.16843300 | -0.33029700 |
| C    | 2.34794800  | 0.27012000  | 0.10534800  |
| C    | 3.02794700  | -1.98886000 | -0.37767600 |
| C    | 4.34226100  | -1.52434200 | -0.50628200 |
| C    | 3.64398900  | 0.77445300  | -0.01754400 |
| O    | 1.26233900  | 1.05371400  | 0.40172400  |
| N    | -3.51374700 | 0.44134100  | -0.31901800 |
| C    | -3.74609100 | 1.74383700  | -0.92240800 |
| O    | -4.71512500 | -0.06132300 | 0.21559000  |
| C    | -5.02883400 | -1.33123500 | -0.36350800 |
| C    | 3.93446600  | 2.23973800  | 0.17973000  |
| H    | 3.41257600  | 2.85603400  | -0.56325500 |
| H    | 5.00664800  | 2.44237000  | 0.09539900  |
| H    | 3.59665600  | 2.58365500  | 1.16485400  |
| H    | -4.50186800 | 1.63744400  | -1.70493400 |
| H    | -2.82517000 | 2.11189600  | -1.37677100 |
| H    | -4.10359600 | 2.47249700  | -0.18277500 |
| H    | -5.10388000 | -1.26176300 | -1.45631700 |
| H    | -6.00316600 | -1.59579900 | 0.05532400  |
| H    | -4.28557300 | -2.08089100 | -0.07842200 |
| H    | -1.16523700 | 1.85366600  | 0.33203800  |
| H    | 0.04104200  | -1.43517000 | -0.86084200 |
| H    | 0.23221200  | -2.01652800 | 0.79152600  |
| H    | 2.79767500  | -3.04219400 | -0.51703300 |
| H    | 5.66202300  | 0.17402800  | -0.43197600 |
| H    | 5.14227600  | -2.22022700 | -0.74269200 |
| H    | -0.01399500 | 0.11934200  | 1.73100700  |
| H    | -0.95556400 | 0.83827600  | -1.08990400 |

**Benzothiadiazine catalyst C**

Zero-point vibrational energy 976455.3 (Joules/Mol)

233.37843 (Kcal/Mol)

Zero-point correction= 0.371912 (Hartree/Particle)

Thermal correction to Energy= 0.392165

Thermal correction to Enthalpy= 0.393109

Thermal correction to Gibbs Free Energy= 0.322992
Sum of electronic and zero-point Energies = \(-1352.060099\)
Sum of electronic and thermal Energies = \(-1352.039846\)
Sum of electronic and thermal Enthalpies = \(-1352.038902\)
Sum of electronic and thermal Free Energies = \(-1352.109019\)

\(E(\text{RB3LYP}) = \ -1352.43201124\)
\(E(\text{RB3LYP/6-311+G**}) = \ -1352.71927733\)

| 0 1 | H       | -1.18071200 | 1.46050600 | -0.54854300 |
|-----|---------|-------------|------------|-------------|
| N   | -0.95035900 | 0.46707800 | -0.61002600 |
| C   | 3.17907900 | -0.08418300 | 0.13971300 |
| C   | -2.06264000 | -0.34047100 | -0.09871100 |
| C   | -4.54497800 | -0.24861100 | 0.36642600 |
| C   | -3.45873500 | -2.43391900 | -0.34029500 |
| C   | -4.73831400 | -1.58543100 | -0.37002800 |
| C   | -2.24899700 | -1.65389600 | -0.87611500 |
| C   | -3.33940600 | 0.52550800 | -0.20466700 |
| H   | -4.38676900 | -0.44302000 | 1.43581700 |
| H   | -3.25565600 | -2.75230200 | 0.69222200 |
| H   | -5.01643600 | -1.38391100 | -1.41492000 |
| H   | -2.39376800 | -1.41510400 | -1.93911000 |
| H   | -3.52067100 | 0.67808200 | -1.27877400 |
| H   | -1.87085800 | -0.59486600 | 0.95350800 |
| H   | -5.45293900 | 0.36221500 | 0.28653800 |
| H   | -3.59715100 | -3.35118700 | -0.92487100 |
| H   | -5.57585200 | -2.13782000 | 0.07368000 |
| H   | -1.33747200 | -2.25227400 | -0.79712000 |
| N   | -3.10162500 | 1.88135400 | 0.33402300 |
| C   | -4.04227800 | 2.87672000 | -0.17128300 |
| H   | -3.71051200 | 3.87540300 | 0.13448300 |
| H   | -5.07447200 | 2.74055900 | 0.19804200 |
| H   | -4.06455600 | 2.84570800 | -1.26575400 |
| C   | -2.98222700 | 1.96018300 | 1.79003700 |
| H   | -2.25526000 | 1.22890200 | 2.15387100 |
| H   | -3.93573000 | 1.79243400 | 2.31954600 |
| H   | -2.62006800 | 2.95728700 | 2.06387000 |
| N   | 0.63460800  | -0.94213000 | 0.33469200 |
|   |   |   |   |
|---|---|---|---|
| C | 0.34841100 | 0.12550900 | -0.36004600 |
| N | 1.27692500 | 1.00558500 | -0.88499500 |
| C | 2.62629000 | 1.02011600 | -0.52252900 |
| H | 0.93280800 | 1.75589500 | -1.46832300 |
| C | 4.50386500 | -0.06266700 | 0.57597900 |
| C | 5.29919000 | 1.05093800 | 0.32006200 |
| H | 6.33329400 | 1.06948200 | 0.64979700 |
| C | 4.75889600 | 2.14299800 | -0.3686800 |
| H | 5.37493900 | 3.01371800 | -0.57474200 |
| C | 3.42953400 | 2.13961000 | -0.77951800 |
| H | 3.00667500 | 3.00267500 | -1.28855400 |
| H | 4.89363500 | -0.92427000 | 1.10869700 |
| S | 2.17869600 | -1.55323000 | 0.30893800 |
| O | 2.35049100 | -2.36343700 | -0.90424200 |
| O | 2.45768700 | -2.15581800 | 1.61294700 |

**Thiourea catalyst A**

Zero-point vibrational energy = 966825.3 (Joules/Mol)

\[
\text{Zero-point correction} = 0.368244 \text{ (Hartree/Particle)}
\]

\[
\text{Thermal correction to Energy} = 0.386912
\]

\[
\text{Thermal correction to Enthalpy} = 0.387856
\]

\[
\text{Thermal correction to Gibbs Free Energy} = 0.320181
\]

Sum of electronic and zero-point Energies = -1147.532254

Sum of electronic and thermal Energies = -1147.513586

Sum of electronic and thermal Enthalpies = -1147.512642

Sum of electronic and thermal Free Energies = -1147.580317

\[
E(\text{RB3LYP}) = -1147.90049817
\]

\[
E(\text{RB3LYP/6-311+G**}) = -1148.12987606
\]
|     | x         | y         | z         |
|-----|-----------|-----------|-----------|
| C   | -3.58843100 | -2.26830400 | -0.39517300 |
| C   | -4.65618500 | -1.16908300 | -0.50229200 |
| C   | -2.21036500 | -1.77193900 | -0.85805700 |
| C   | -2.84929600 | 0.59820100  | -0.28791800 |
| H   | -4.16468500 | -0.07977200 | 1.30546900  |
| H   | -3.51659000 | -2.60559800 | 0.64879700  |
| H   | -4.83289800 | -0.93724700 | -1.56300900 |
| H   | -2.23397900 | -1.52824200 | -1.92980400 |
| H   | -2.93781700 | 0.74058400  | -1.37556900 |
| H   | -1.74494100 | -0.78666300 | 0.99041200  |
| H   | -4.97247300 | 0.90130900  | 0.08437200  |
| H   | -3.88640000 | -3.14490300 | -0.98331600 |
| H   | -5.61300800 | -1.52305600 | -0.09843700 |
| H   | -1.45314200 | -2.54775700 | -0.71575100 |
| N   | -2.36525900 | 1.89650700  | 0.22091700  |
| C   | -3.07921200 | 3.03969000  | -0.33693600 |
| H   | -2.55563400 | 3.96228500  | -0.06173000 |
| H   | -4.12241800 | 3.13055500  | 0.01588200  |
| H   | -3.09458500 | 2.97028100  | -1.42998000 |
| C   | -2.25703300 | 1.99427400  | 1.67569800  |
| H   | -1.67021500 | 1.16060600  | 2.07092800  |
| H   | -3.23356900 | 2.00614200  | 2.19031700  |
| H   | -1.73409000 | 2.92236200  | 1.93128800  |
| C   | 0.70547500  | -0.47304100 | -0.04254700 |
| N   | 1.74826200  | 0.30009300  | -0.51137300 |
| C   | 3.14212700  | 0.22594300  | -0.28783600 |
| H   | 1.49788000  | 0.89792800  | -1.29046900 |
| C   | 5.09948800  | -0.16559700 | 1.07297900  |
| C   | 5.93155300  | 0.26253600  | 0.03725000  |
| H   | 7.01013300  | 0.27163100  | 0.16596100  |
| C   | 5.36052600  | 0.68140400  | -1.16523400 |
| H   | 5.98981700  | 1.02000900  | -1.98393400 |
| C   | 3.97766200  | 0.65985000  | -1.32864400 |
| H   | 3.53816200  | 0.97508900  | -2.27324900 |
| H   | 5.53026400  | -0.48755800 | 2.01738400  |
| S   | 0.86414900  | -1.84618900 | 0.91102800  |
| H   | 3.07725900  | -0.50944200 | 1.73639900  |
TS (catalyst C)

Zero-point vibrational energy
1725582.1 (Joules/Mol)
412.42401 (Kcal/Mol)

Zero-point correction= 0.657240 (Hartree/Particle)
Thermal correction to Energy= 0.695225
Thermal correction to Enthalpy= 0.696169
Thermal correction to Gibbs Free Energy= 0.586205

Sum of electronic and zero-point Energies= -2137.750701
Sum of electronic and thermal Energies= -2137.712716
Sum of electronic and thermal Enthalpies= -2137.711772
Sum of electronic and thermal Free Energies= -2137.821735

E(RB3LYP) = -2138.40794093
Imaginary frequency = 190i
E(RB3LYP/6-311+G**) = -2138.91153758

0 1

C -1.84435200 -1.64002000 1.84192400
C -0.97765600 -0.80910600 2.60484800
C 0.40828500 -0.99040600 2.54053300
O 0.97669500 -1.91329500 1.86670600
C -3.29452800 -1.81486100 2.28460800
C -4.13701800 -1.85166900 1.03336300
C -5.32780400 -1.62136600 -1.46042000
C -3.41199400 -1.34318300 -0.05486700
C -5.45830900 -2.25267500 0.87169000
C -6.05671700 -2.13967900 -0.38753100
C -3.99422200 -1.21074700 -1.32699800
H 0.32943800 5.73331500 -0.96676500
C -0.39509700 5.00540200 -0.61552400
C -2.22947400 3.07121700 0.25195500
C -0.03646000 3.65740700 -0.58256900
C -1.66680200 5.39040100 -0.20140500
C -2.57352200 4.41868900 0.24049800
C -0.94976700 2.67674100 -0.16821500
H -1.95194100 6.43778900 -0.21918900
H -3.56691300 4.71334800 0.56720400
TS (catalyst A)

Zero-point vibrational energy 1716626.6 (Joules/Mol)

410.28361 (Kcal/Mol)

Zero-point correction= 0.653829 (Hartree/Particle)
Thermal correction to Energy= 0.690259
Thermal correction to Enthalpy= 0.691204
Thermal correction to Gibbs Free Energy= 0.583293

Sum of electronic and zero-point Energies= -1933.217289
Sum of electronic and thermal Energies= -1933.180858
Sum of electronic and thermal Enthalpies= -1933.179914
Sum of electronic and thermal Free Energies= -1933.287824

E(RB3LYP) = -1933.87111706
Imaginary frequency = 208i

E(RB3LYP/6-311+G**) = -1934.31737508
| Element | X         | Y         | Z         |
|---------|-----------|-----------|-----------|
| H       | 2.53880400| 0.06344000| 1.05638100|
| H       | 2.51839700| -0.65205900| -2.15875800|
| H       | -0.43808100| 3.24733900| -2.82108000|
| S       | 1.24820600| 1.36645100| -2.93861400|