Supporting information

Diastereoselective Synthesis of Tetrahydrobenzo[b]azocines by $Lu(OTf)_3$ Catalyzed [4 + 4] Cycloaddition of Donor–Acceptor Cyclobutanes with Anthranils

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Note added after first publication: This ESI has been updated with the corrected version of compound 4. This ESI replaces that originally published on 27 April 2022.

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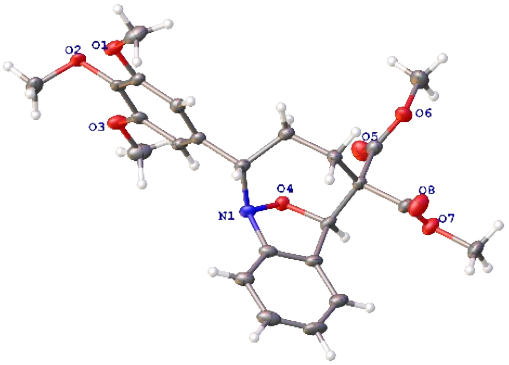
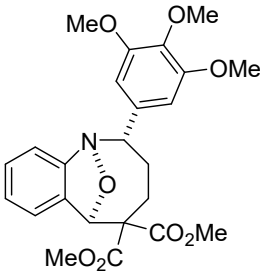
General information.

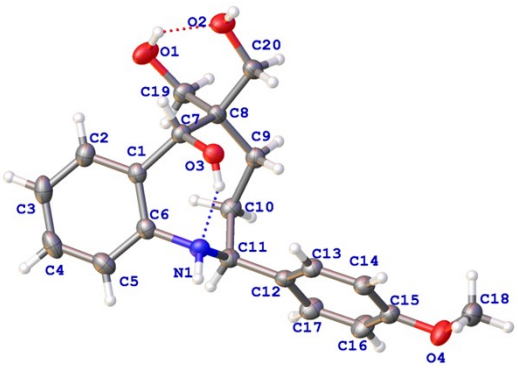
^1H NMR spectra, ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in chloroform-d_3, acetone-d_6 or dmso-d_6. All signals are reported in ppm with the internal TMS signal at 0 ppm as a standard. The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. All solvents were freshly distilled from CaH_2 prior to use. Lewis-acid purchased from Accela ChemBio Co. Ltd or J&K or Energy Chemical Company were used directly. 4 Å molecular sieves purchased from Sinopharm Chemical Reagent Co.,Ltd were powdered and dried at 300 °C in muffle furnace for 8-10 hours prior to use. Bisoxazoline ligand (bis(S)-4-isopropyl-4,5-dihydrooxazol-2-yl)methane) was purchased from Energy Chemical Company and used directly.

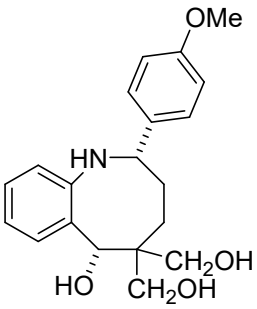




3ao

Figure 1. X-ray crystal structure of compound **3ao** (CCDC 2142610).



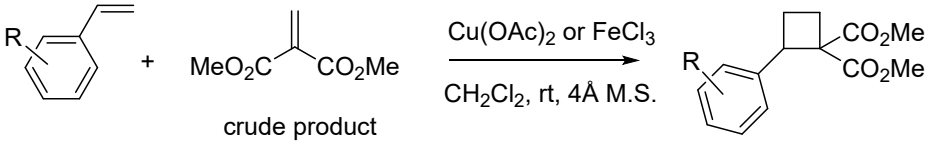


6

Figure 2. X-ray crystal structure of compound **6** (CCDC 2164577).

Synthesis of substrates.

Cyclobutanes **2** were synthesized according to our previous method. And the spectral data of cyclobutanes are consisted with the literature.[1]

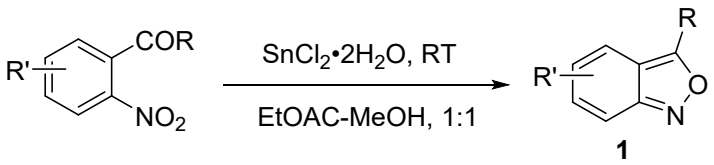


2

A flame-dried schlenk tube (50 mL) was evacuated and recharged with N_2 for 3 times.

Under N_2, the tube (50 mL) was charged with catalytic $Cu(OAc)_2$ or $FeCl_3$, 200 mg of activated 4Å molecular sieves powder (M S), dry CH_2Cl_2 (3 mL) at room temperature. In another flame-dried schlenk tube (25 mL), substituted styrene (10 mmol) were dissolved in dry CH_2Cl_2 (6 mL) and cooled to 0 °C for 10 min. Then a solution of crude dimethyl methylidenemalonate (unpurified product, 20 mmol, 2 equiv, 2.90 g. Mass calculation based on pure dimethyl methylidene malonate molecular mass) in dry CH_2Cl_2 (6 mL) was added to the solution of 1-methoxy-4-vinylbenzene **1a** via syringe at 0 °C. This mixed solution was then added dropwise to the $Cu(OAc)_2$ solution via syringe in three portions (4 mL/portion) every 10 min. After the addition was complete, the reaction mixture was stirred at rt for 4 hours until the reaction was complete (monitored by TLC). The reaction mixture was quenched with Et_3N (2-3 mL), and then passed over a short pad of silica gel with 50 mL of CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (silica gel was pretreated with 1-2% Et_3N in Hexanes), eluting with (hexanes:AcOEt = 10:1) to afford cyclobutane **2**.

Anthranils **1** were synthesized according to the literature, and the spectral data refer to the literature.[2]

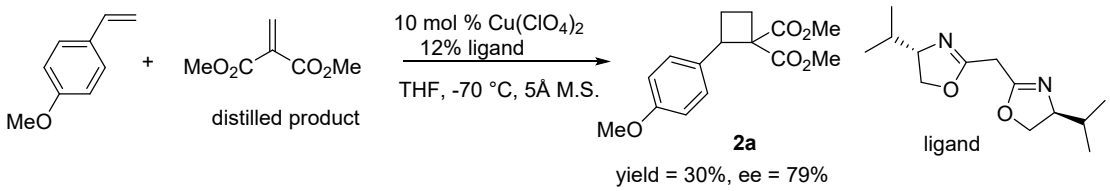


1

The substrate was dissolved in a 1:1 mixture of EtOAc/MeOH at 0.1 M. $SnCl_2 \cdot 2H_2O$ (3 equiv.) was added, and the reaction mixture was stirred at room temperature for 20 h. TLC confirmed all starting material had been consumed. If necessary, the reaction solvent was reduced to ca. 10 ml on a rotary evaporator, and then the crude material was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer

was extracted thrice with CH_2Cl_2. The organic portions were combined, washed with saturated aqueous $NaHCO_3$, water, brine, and then dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography, eluting with hexanes and EtOAc to afford anthranils **1**.

Chiral cyclobutane **2a** (ee = 79%) was synthesized according to the literature by using bis[(4S)-(1-methylethyl)oxazolin-2-yl]methane as ligand.[3]



A mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.04 mmol) and ligand (L9, 0.05 mmol) in THF (3 mL) with activated 5 Å MS was stirred at room temperature for 1.5 h under atmosphere of nitrogen. Then the mixture was cooled to -70 °C for 30 minutes, and distilled dimethyl methylene malonate (1.0 mmol) was mixed with 4-methoxy styrene (0.40 mmol) in 1 mL of THF, cooled to -70 °C, and added to the reaction mixture while cold. The resulting solution was stirred until the styrene was completely consumed (monitored by TLC, hexane/ethyl acetate = 5/1). Then the mixture was quenched with Et_3N at -70 °C, then passed through a short silica gel column and eluted with DCM. The combined elution was concentrated under reduced pressure to give the crude product which was further purified by flash chromatography on silica gel to give cyclobutane **2a** in 30% yield with 79% ee value, determined by HPLC, chiralcel ADH, *i*-PrOH/hexane =98/2, 0.6 mL/min, 240 nm; $t_{r(minor)}$ = 13.6 min, $t'_{r(major)}$ = 15.2 min).

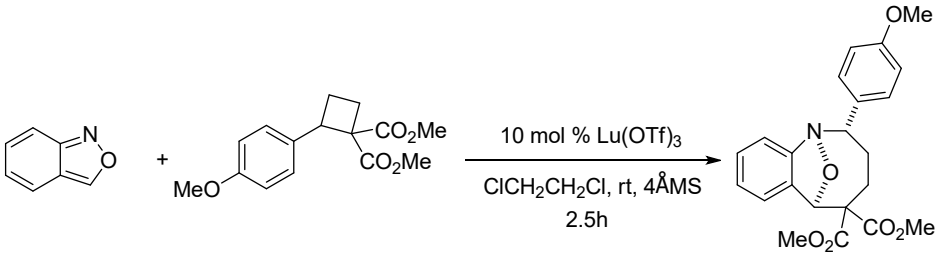
Reference

1. H. Luo, J. Yan, Z. Chen, Y. Wei, B. Chen and Y. Liu, *ChemistrySelect*. 2020, **5**, 4074-4077.

2. J. Chauhan and S. Fletcher, *Tetrahedron Lett.*, 2012, **53**, 4951-4954.

3. J. Hu, L. Feng, L. Wang, Z. Xie, Y. Tang and X. Li, *J. Am. Chem. Soc.*, 2016, **138**, 13151-13154.

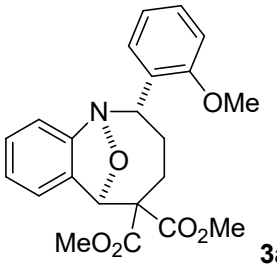
1. Typical procedure for $Lu(OTf)_3$ catalyzed [4+4] cycloaddition reaction.



1a **2a** **3aa**

A flame-dried schlenk tube (25 mL) was evacuated and recharged with N_2 for 3 times. Under N_2, the tube was charged with 10 mol % $Lu(OTf)_3$, 45 mg of activated 4Å molecular sieves powder (M S), benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg), dry $ClCH_2CH_2Cl$ (1.5 mL) at room temperature (rt). The reaction mixture was stirred at rt for 2.5 hours until the reaction was complete (monitored by TLC, hexanes:AcOEt = 5:1). The reaction mixture was passed over a plug of silica gel with 10 mL of CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography, eluting with (hexanes:AcOEt = 8:1) to afford 44.8 mg (75%) of **3aa**, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2 H), 7.30-7.28 (m, 1H), 7.05-7.01 (m, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 6.90-6.87 (m, 3 H), 6.24 (s, 1 H), 4.23 (t, *J* = 6.8 Hz, 1 H), 3.811 (s, 3 H), 3.806 (s, 3 H), 3.80 (s, 3 H), 2.38-2.33 (m, 1 H), 2.12-2.06 (m, 2 H), 1.73-1.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.7, 158.6, 152.5, 135.9, 129.5, 129.1, 127.3 (2C), 124.0, 121.8, 113.8 (2C), 112.5, 84.5, 74.8, 64.1, 55.3, 53.1, 52.7, 33.0, 26.6 ; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{23}NO_6H$: 398.1604, found: 398.1602.

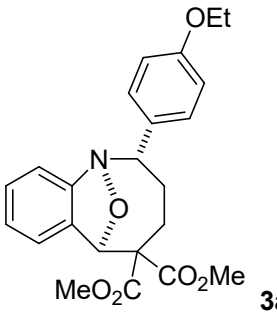
1. Synthesis of 3ab



3ab

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2b** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 20 h, eluting with (hexanes:AcOEt = 7:1) to afford 41.6 mg (68%) of **3ab** (*dr*>99:1), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 1 H), 7.23-7.15 (m, 2 H), 6.97-6.93 (m, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 7.2 Hz, 2 H), 6.19 (s, 1 H), 4.64 (dd, *J* = 10.4 Hz, 5.2 Hz, 1 H), 3.76 (s, 3 H), 3.73 (s, 6 H), 2.33-2.27 (m, 1 H), 2.16-2.09 (m, 1 H), 1.92-1.86 (m, 1 H), 1.64-1.58 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.8, 155.1, 152.8, 132.2, 129.4, 128.9, 127.9, 127.85, 123.8, 121.6, 121.1, 112.7, 109.9, 84.6, 69.1, 64.2, 55.2, 53.1, 52.7, 30.9, 26.7; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{23}NO_6H$: 398.1604, found: 398.1606.

2. Synthesis of 3ad

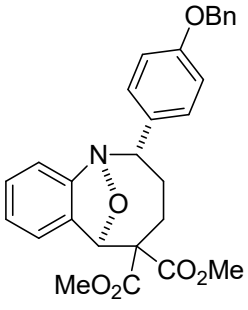


3ad

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2d** (0.15 mmol, 44 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 4 h, eluting with (hexanes:AcOEt = 8:1) to afford 41.7 mg (65%) of **3ad** (*dr*=9:1), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 2 H), 7.30-7.26 (m, 1 H), 7.05-7.00 (m, 1 H), 6.94 (d, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 3 H), 6.24 (s, 1 H), 4.23 (t, *J* = 7.2 Hz, 1 H), 4.03 (q, *J* = 14.0 Hz, 7.2 Hz, 2 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.38-2.33 (m, 1 H), 2.12-2.06 (m, 2 H), 1.72-1.65 (m, 1 H), 1.41 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.7, 157.9, 152.5, 135.8, 129.5, 129.0, 127.3 (2C),

123.9, 121.7, 114.4 (2C), 112.5, 84.5, 74.8, 64.1, 63.5, 53.1, 52.7, 33.0, 26.6, 14.8; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{23}H_{25}NO_6H$: 412.1760, found: 412.1761.

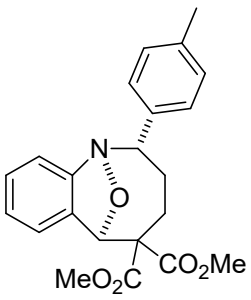
3. Synthesis of 3ae



3ae

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2e** (0.15 mmol, 53.3 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 18 h, eluting with (hexanes:AcOEt = 8:1) to afford 51.7 mg (73%) of **3ae** (*dr*=13:1), light white oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2 H), 7.32-7.29 (m, 4 H), 7.26-7.18 (m, 2 H), 6.97-6.93 (m, 1 H), 6.90-6.88 (m, 2 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.17 (s, 1 H), 4.99 (s, 2 H), 4.16 (t, *J* = 7.2 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 2.31-2.26 (m, 1 H), 2.04-1.99 (m, 2 H), 1.65-1.58 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 157.8, 152.4, 137.1, 136.2, 129.5, 129.0, 128.5 (2C), 127.9, 127.43 (2C), 127.36 (2C), 124.0, 121.7, 114.8 (2C), 112.4, 84.5, 74.7, 70.0, 64.1, 53.1,52.7, 32.9, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{28}H_{27}NO_6H$: 474.1917, found: 474.1920.

4. Synthesis of 3af

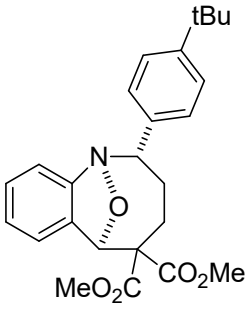


3af

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2f** (0.15 mmol, 39.3 mg) and 45 mg of 4Å M.S. and 20 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was

carried out at 60°C for 3d, eluting with (hexanes:AcOEt = 8:1) to afford 16.1 mg (30%) of **3af** (*dr*=20:1), yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2 H), 7.30-7.26 (m, 1 H), 7.17 (d, *J* = 7.6 Hz, 2 H), 7.04-7.01 (m, 1 H), 6.94-6.87 (m, 2 H), 6.25 (s, 1 H), 4.24 (t, *J* = 7.6 Hz, 1 H), 3.802 (s, 3 H), 3.798 (s, 3 H), 2.40-2.36 (m, 1 H), 2.34 (s, 3 H), 2.12-2.07 (m, 2 H), 1.73-1.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.5, 140.7, 136.6, 129.5, 129.1 (2C), 129.05, 126.1 (2C), 123.9, 121.8, 112.9, 84.6, 75.1, 64.1, 53.1, 52.7, 33.0, 26.6, 21.0; HRMS-TOF-ES^{+}: $[M+H]^{+}$ calcd for $C_{22}H_{23}NO_5H$: 382.1654, found: 382.1655.

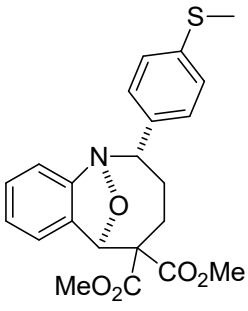
5. Synthesis of 3ag



3ag

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2g** (0.15 mmol, 45.6 mg) and 45 mg of 4Å M.S. and 30 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at 60°C for 17h, eluting with (hexanes:AcOEt =7:1) to afford 36.1 mg (57%) of **3ag** (*dr*=25:1), yellow oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 4 H), 7.29-7.26 (m, 1 H), 7.04-7.00 (m, 1 H), 6.90 (dd, *J* = 18.8 Hz, 8.0 Hz, 2 H), 6.25 (s, 1 H), 4.26 (t, *J* = 8.0 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.41-2.35 (m, 1 H), 1.92-1.86 (m, 2 H), 1.72-1.65 (m, 1 H) , 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 167.7, 152.6, 149.9, 140.7, 129.5, 129.1, 125.9, 125.4, 123.9, 121.8, 112.5, 84.6, 75.0, 64.2, 53.1, 52.7, 34.5, 32.9, 31.4, 26.7; HRMS-TOF-ES^{+}: $[M+H]^{+}$ calcd for $C_{25}H_{29}NO_5H$: 424.2124, found: 424.2127.

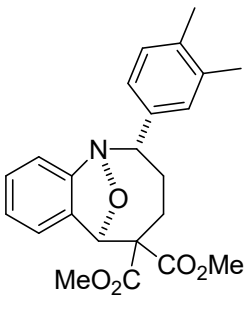
6. Synthesis of 3ah



3ah

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2h** (0.15 mmol, 42.5 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 24h, eluting with (hexanes:AcOEt =7:1) to afford 32.9 mg (55%) of **3ah** (*dr*=50:1), yellow oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2 H), 7.30-7.24 (m, 3 H), 7.05-7.01 (m, 1 H), 6.90 (dd, *J* = 16.8 Hz, 8.0 Hz, 2 H), 6.25 (s, 1 H), 4.24 (t, *J* = 8.0 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.48 (s, 3 H) , 2.39-2.33 (m, 1 H), 2.10-2.04 (m, 2 H), 1.73-1.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.3, 149.9, 140.7, 136.9, 129.6, 129.1, 127.0, 126.8, 124.1, 121.8, 112.5, 84.6, 74.8, 64.1, 53.2, 52.8, 47.0, 32.8, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{23}NO_5SH$: 414.1375, found: 414.1377.

7. Synthesis of 3ak

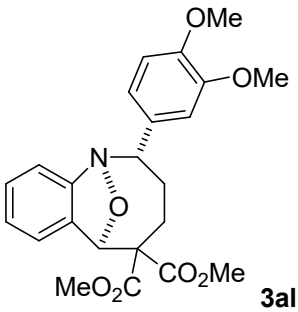


3ak

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2k** (0.15 mmol, 41.5 mg) and 45 mg of 4Å M.S. and 20 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at 60°C for 37h, eluting with (hexanes:AcOEt =7:1) to afford 31.4 mg (52%) of **3ak** (*dr*=11:1), colorless oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2 H), 7.18-7.11 (m, 2 H), 7.04-7.00 (m, 1 H), 6.94-6.87 (m, 2 H), 6.25 (s, 1 H), 4.22 (t, *J* = 7.8 Hz, 1 H), 3.804 (s, 3 H), 3.801 (s, 3 H), 2.40-2.35 (m, 1 H), 2.28 (s, 3 H), 2.25 (s, 3 H), 2.13-2.07 (m, 2 H), 1.72-1.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.6,

141.2, 136.7, 135.2, 129.7, 129.5, 129.0, 127.4, 123.9, 123.6, 121.7, 112.5, 84.6, 75.2, 64.1, 53.1, 52.7, 33.0, 26.7, 19.8, 19.4; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{23}H_{25}NO_5H$: 396.1811, found: 396.1814.

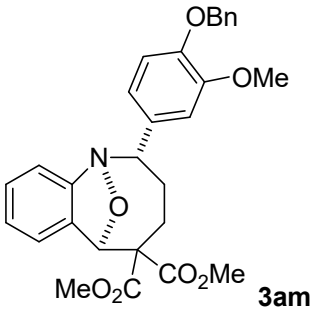
8. Synthesis of 3al



3al

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2l** (0.15 mmol, 46.4 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 4h, eluting with (hexanes:AcOEt =7:1) to afford 43.2 mg (66%) of **3al** (*dr*=7:1), colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 1 H), 7.06-7.05 (m, 1 H), 7.03-7.00 (m, 1 H), 6.97-6.94 (m, 2 H), 6.89 (d, *J* = 7.2 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 6.25 (s, 1 H), 4.24 (t, *J* = 11.2 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.39-2.34 (m, 1 H), 2.13-2.08 (m, 2 H), 1.73-1.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.3, 149.0, 148.0, 136.4, 129.5, 129.0, 124.0, 121.8, 118.1, 112.4, 111.0, 109.6, 84.5, 74.9, 64.1, 55.94, 55.91, 53.1, 52.7, 32.9, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{23}H_{25}NO_7H$: 428.1709, found: 428.1716.

9. Synthesis of 3am

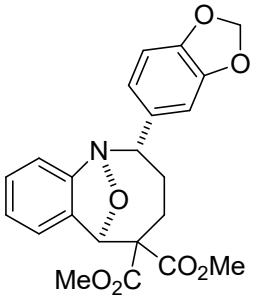


3am

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2m** (0.15 mmol,

57.6 mg) and 45 mg of 4Å M.S. and 20 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 48h, eluting with (hexanes:AcOEt =7:1) to afford 43 mg (58%) of **3am** (*dr*=8:1), yellow oily liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 2 H), 7.31-7.27 (m, 2 H), 7.23-7.20 (m, 2 H), 7.01 (d, *J* = 1.6 Hz, 1 H), 6.97-6.93 (m, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.82-6.78 (m, 3 H), 6.16 (s, 1 H), 5.08 (s, 2 H), 4.14 (t, *J* = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 2.32-2.26 (m, 1 H), 2.04-1.99 (m, 2 H), 1.64-1.57 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.3, 149.7, 147.1, 137.3, 137.0, 129.5, 129.0, 128.5 (2C), 127.7, 127.2 (2C), 124.0, 121.8, 118.2, 114.0, 112.4, 110.2, 84.5, 74.9, 71.1, 64.0, 56.1, 53.1, 52.7, 32.8, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{29}H_{29}NO_7H$: 504.2022, found: 504.2018.

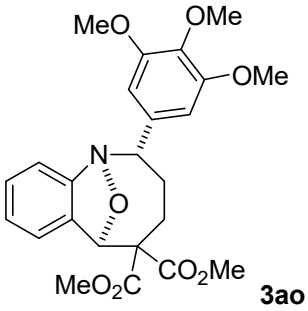
10. Synthesis of 3an



3an

The reaction of benzoxazole **1a** (0.225 mmol,26.8 mg), cyclobutane **2n** (0.15 mmol, 43.9 mg) and 45 mg of 4 Å M.S. and 20 mol % Lu$(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 12 h, eluting with (hexanes:AcOEt=7:1) to afford 25 mg (41%) of **3an** (*dr*=20:1), colorless liquid.^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 1 H) , 7.05-7.01 (m, 2 H), 6.93 (d, *J* = 8.0 Hz, 1 H) , 6.89-6.85 (m, 2 H) , 6.77 (d, *J* = 8.0 Hz, 1 H), 6.24 (s, 1 H) , 5.94 (s, 2 H), 4.24 (dd, *J* = 6.0 Hz, 9.6 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.39-2.34 (m, 1 H), 2.11-2.05 (m, 2 H), 1.70-1.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 167.7, 152.4, 147.8, 146.5, 137.8, 129.6, 129.0, 124.1, 121.8, 119.3, 112.4, 108.0, 107.1, 100.9, 84.6, 84.6, 64.1, 53.2, 52.7, 33.1, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{21}NO_7H$: 412.1396, found: 412.1399.

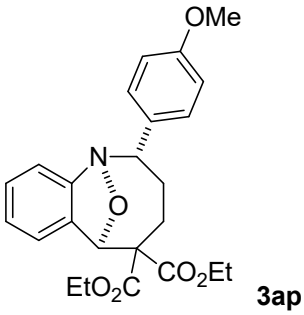
11. Synthesis of 3ao



3ao

The reaction of benzoxazole **1a** (0.225 mmol,26.8 mg), cyclobutane **2o** (0.15 mmol, 50.7 mg) and 45 mg of 4 Å M.S. and 20 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 17 h, eluting with (hexanes:AcOEt=7:1) to afford 54.7 mg (80%) of **3ao** (*dr*=13:1), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 1 H), 7.06-7.02 (m, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 6.70 (s, 2 H), 6.25 (s, 1 H), 4.22 (t, *J* = 8.0 Hz, 1 H), 3.90 (s, 6 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.41-2.36 (m, 1 H), 2.14-2.09 (m, 2 H), 1.72-1.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.6, 153.2, 152.3 (2C), 139.4, 136.9, 129.5, 129.0, 124.1, 121.8, 112.4, 103.2 (2C), 84.6, 75.3, 64.0, 60.8, 56.2 (2C), 53.1, 52.8, 32.9, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{24}H_{27}NO_8H$:458.1815, found:458.1820.

12. Synthesis of 3ap

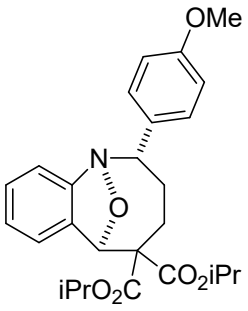


3ap

The reaction of benzoxazole **1a** (0.225 mmol,26.8 mg), cyclobutane **2p** (0.15 mmol, 46 mg) and 45 mg of 4 Å M.S. and 20 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 14 h, eluting with (hexanes:AcOEt=7:1) to afford 51.8 mg (81%) of **3ao** (*dr*=13:1), white liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2 H), 7.22-7.18 (m, 1 H), 6.97-6.93 (m, 1 H), 6.88-6.81 (m, 4 H), 6.16 (s, 1 H), 4.23-4.13 (m, 5 H), 3.73 (s, 3 H), 2.30-2.25 (m, 1 H), 2.06-1.99 (m, 2 H), 1.64-1.57 (m, 1 H), 1.25-1.19 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.3, 158.6, 152.5, 136.1, 129.4, 129.2, 127.4 (2C),

123.9, 121.9, 113.8 (2C), 112.4, 84.5, 74.8, 64.1, 61.9, 61.8, 55.3, 33.0, 26.5, 14.1(2C); HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{24}H_{27}NO_6H$: 426.1917, found: 426.1922.

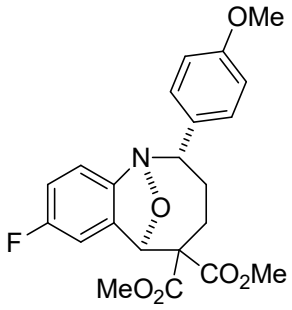
13. Synthesis of 3aq



3aq

The reaction of benzoxazole **1a** (0.225 mmol, 26.8 mg), cyclobutane **2q** (0.15 mmol, 50.3 mg) and 45 mg of 4Å M.S. and 20 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 14h, eluting with (hexanes:AcOEt = 8:1) to afford 49.7 mg (73%) of **3aq** (*dr*=10:1), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2 H), 7.20-7.18 (m, 1 H), 6.96-6.92 (m, 1 H), 6.88-6.85 (m, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 6.13 (s, 1 H), 5.09-5.00 (m, 2 H), 4.14 (dd, *J* = 10.0 Hz, 5.6 Hz, 1 H), 3.73 (s, 3 H), 2.27-2.22 (m, 1 H), 2.05-1.95 (m, 2 H), 1.60-1.56 (m, 1 H), 1.30 (d, *J* = 6.0 Hz, 3 H), 1.20-1.15 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 166.8, 158.5, 152.6, 136.3, 129.3, 129.2, 127.4 (2C), 123.8, 121.9, 113.8 (2C), 112.4, 84.5, 75.0, 69.5, 69.3, 64.1, 55.3, 33.1, 26.5, 21.8, 21.6 (3C); HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{26}H_{31}NO_6H$: 454.2230, found: 454.2229.

14. Synthesis of 3ba

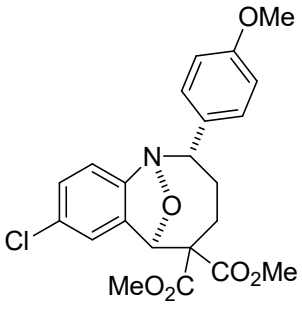


3ba

The reaction of anthranil **1b** (0.225 mmol, 30.8 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was

carried out at rt for 2h, eluting with (hexanes:AcOEt = 8:1) to afford 29.1 mg (46%) of **3ba** (*dr*=7:1), white liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 2 H), 6.94-6.89 (m, 1 H), 6.83-6.80 (m, 3 H), 6.55-6.53 (m, 1 H), 6.15 (s, 1 H), 4.11 (t, *J* = 7.2 Hz, 1 H), 3.74 (s, 6 H), 3.73 (s, 3 H), 2.36-2.30 (m, 1 H), 2.05-2.00 (m, 2 H), 1.68-1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.6, 158.6, 148.5, 135.6, 127.3 (2C), 116.4 116.1, 113.8 (2C), 109.6, 109.4, 84.6, 84.6, 74.9, 63.9, 55.3, 53.2, 52.9, 32.8, 26.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.36; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6FH$: 416.1509, found: 416.1510.

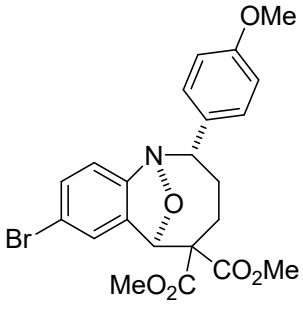
15. Synthesis of 3ca



3ca

The reaction of anthranil **1c** (0.225 mmol, 34.6 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 15 h, eluting with (hexanes:AcOEt = 8:1) to afford 35.9 mg (55%) of **3ca** (*dr*=33:1), yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.8 Hz, 2 H), 7.24 (d, *J* = 2.0 Hz, 1 H), 6.90-6.85 (m, 4 H), 6.22 (s, 1 H), 4.19 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 6 H), 3.80 (s, 3 H), 2.44-2.38 (m, 1 H), 2.13-2.08 (m, 2 H), 1.74-1.67 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.5, 158.7, 151.1, 135.5, 131.1, 129.6, 129.2, 127.3 (2C), 122.3, 113.9 (2C), 113.4, 84.4, 74.8, 64.0, 55.3, 53.3, 52.9, 32.9, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6ClH$: 432.1214, found: 432.1213.

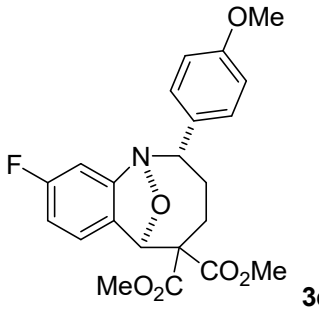
16. Synthesis of 3da



3da

The reaction of anthranil **1d** (0.225 mmol, 44.6 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 14 h, eluting with (hexanes:AcOEt = 8:1) to afford 50.7 mg (67%) of **3da** (*dr*=7:1), yellow oil liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 3 H), 6.94 (d, *J* = 1.6 Hz, 1 H), 6.83-6.81 (m, 2 H), 6.74 (d, *J* = 8.4 Hz, 1 H), 6.15 (s, 1 H), 4.12 (t, *J* = 7.2 Hz, 1 H), 3.74 (m, 6 H), 3.73 (s, 3 H), 2.36-2.31 (m, 1 H), 2.01-2.00 (m, 2 H), 1.67-1.60 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.5, 158.7, 151.6, 135.4, 132.4, 131.5, 127.3 (2C), 125.2, 116.4 113.9 (2C), 113.6, 84.3, 74.8, 64.0, 55.3, 53.3, 52.9, 32.9, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6BrH$: 476.0709, found: 476.0710.

17. Synthesis of 3ea

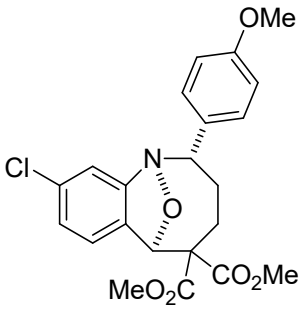


3ea

The reaction of anthranil **1e** (0.225 mmol, 30.8 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 13 h, eluting with (hexanes:AcOEt = 8:1) to afford 31.1 mg (50%) of **3ea** (*dr*=7:1), yellow oil liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.8 Hz, 2 H), 6.83-6.81 (m, 2 H), 6.77-6.74 (m, 1 H), 6.67-6.62 (m, 1 H), 6.59-6.56 (m, 1 H), 6.14 (s, 1 H), 4.15 (t, *J* = 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 2.35-2.29 (m, 1 H), 2.06-2.00 (m, 2 H), 1.66-1.59 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.6, 158.7,

135.4, 127.3 (2C), 122.9, 122.8, 113.9 (2C), 110.9, 110.7, 100.7, 100.4, 84.3, 74.8, 64.1, 55.3, 53.2, 52.8, 33.0, 26.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.31; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6FH$: 416.1509, found: 416.1510.

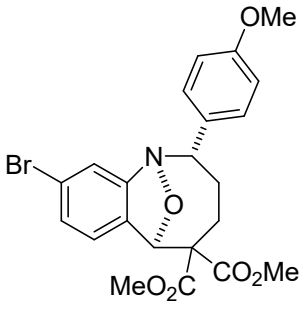
18. Synthesis of 3fa



3fa

The reaction of anthranil **1f** (0.225 mmol, 34.6 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at rt for 14 h, eluting with (hexanes:AcOEt = 8:1) to afford 43.9 mg (65%) of **3fa** (*dr*=10:1), white oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2 H), 7.02-6.99 (m, 1 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.90-6.88 (m, 2 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.22 (s, 1 H), 4.22 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.42-2.37 (m, 1 H), 2.27-2.08 (m, 2 H), 1.73-1.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.4, 158.7, 153.9, 135.4, 135.3, 127.7, 127.3 (2C), 124.1, 122.7, 113.9 (2C), 110.9, 84.3, 74.9, 64.0, 55.3, 53.2, 52.8, 33.0, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6ClH$: 432.1214, found: 432.1218.

19. Synthesis of 3ga

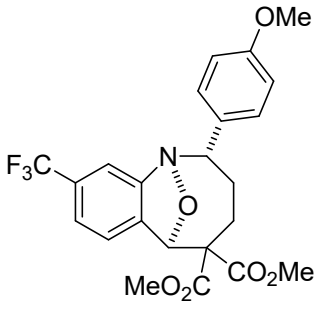


3ga

The reaction of anthranil **1g** (0.225 mmol, 26.8 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4Å M.S. and 10 mol % Lu $(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was

carried out at rt for 14 h, eluting with (hexanes:AcOEt = 7:1) to afford 48.4 mg (67.8%) of **3ga** (*dr*=10:1), yellow oil liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2 H), 7.15 (dd, *J* = 1.6 Hz, 8.0 Hz, 1 H）, 7.09 (d, *J* = 1.6 Hz, 1 H), 6.91-6.87 (m, 2 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.20 (s, 1 H), 4.22 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.42-2.37 (m, 1 H), 2.13-2.09 (m, 2 H), 1.73-1.66 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ169.2, 167.5, 158.7, 154.1, 135.4, 130.3, 128.3, 127.2, 126.9, 123.1, 123.1, 115.8, 113.9, 84.4, 74.9, 63.9, 55.3, 53.2, 52.8, 33.0, 26.5; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6BrH$: 476.0709, found: 476.0710.

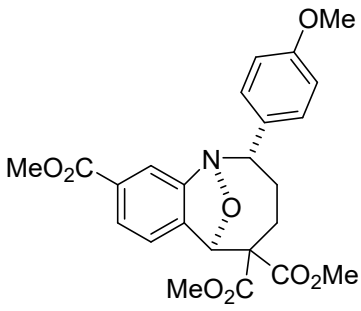
20. Synthesis of 3ha



3ha

The reaction of anthranil **1h** (0.225 mmol,42.1 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4 Å M.S. and 15 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 14 h, eluting with (hexanes : AcOEt=7:1) to afford 33.5 mg (48%) of **3ha** (*dr*=5:1), yellow liquid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.16 (s, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.92-6.88 (m, 2 H), 6.29 (s, 1 H), 4.27 (t, *J* = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.45-2.39 (m, 1 H), 2.15-2.10 (m, 2 H), 1.70-1.63 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.3, 157.7, 152.0, 134.2, 131.9, 129.3, 126.2, 121.4, 120.2, 112.9, 108.5, 83.3, 73.9, 62.9, 54.3, 52.3, 51.9, 32.1, 25.6; ^{19}F NMR(376 MHz, $CDCl_3$) δ -62.40; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6F_3H$: 467.1917, found: 467.1917.

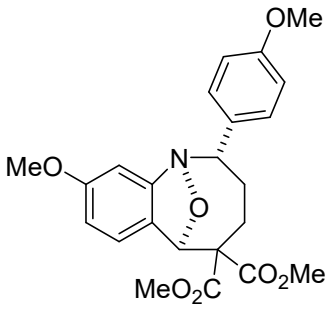
21. Synthesis of 3ia



3ia

The reaction of benzoxazole **1i** (0.225 mmol,39.9 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4 Å M.S. and 10 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 3 h, eluting with (hexanes : AcOEt=7:1) to afford 35 mg (51%) of **3ia** (*dr*=13:1), colorless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1 H), 7.59 (s, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 2 H), 6.28 (s, 1 H), 4.28 (t, *J* = 7.6 Hz, 1 H), 3.90 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 2.41-2.36 (m, 1 H), 2.13-2.08 (m, 2 H), 1.68-1.61 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.4, 166.3, 158.7, 152.9, 135.4, 134.0, 131.9, 127.3, 125.7, 121.8, 113.8, 113.3, 84.4, 74.8, 63.9, 55.3, 53.2, 52.8, 52.3, 33.0, 26.6; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{24}H_{25}NO_8H$: 456.1658, found: 456.1660.

22. Synthesis of 3ja

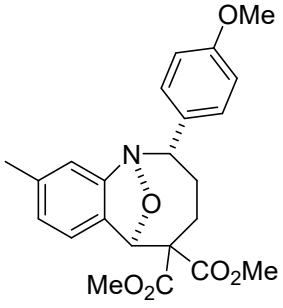


3ja

The reaction of benzoxazole **1j** (0.225 mmol,33.6 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4 Å M.S. and 10 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 mL) was carried out at 10 °C for 4 h, eluting with (hexanes : AcOEt=7:1) to afford 26 mg (41%) of **3ja** (*dr*=5:1), yellow oil.^{1}H NMR (400 MHz, acetone-D_6) δ 7.39 (d, *J* = 8.4 Hz, 2 H), 6.92-6.88 (m, 4 H), 6.51 (s, 1 H), 6.09 (s, 1 H), 4.27 (dd, *J* = 9.6 Hz, 5.2 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 2.31-2.22 (m, 1 H), 2.00-1.97 (m, 2 H), 1.73-1.67 (m, 1 H); ^{13}C NMR (100 MHz, acetone-D_6) δ 168.8, 167.1, 158.2, 156.4, 145.6, 136.0, 130.3, 129.8, 127.0, 114.4, 113.0, 112.5, 107.2, 84.1, 73.7, 63.5, 54.7, 54.2, 52.0,

51.8, 31.9, 26.2; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{23}H_{25}NO_7H$: 428.1709, found: 428.1710.

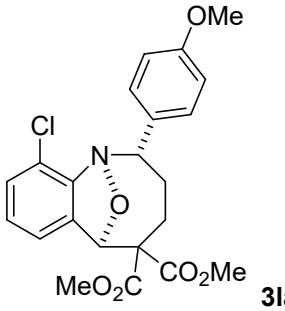
23. Synthesis of 3ka



3ka

The reaction of benzoxazole **1k** (0.225 mmol,29.9 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4 Å M.S. and 10 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 14 h, eluting with (hexanes : AcOEt=7:1) to afford 32.5 mg (53%) of **3ka** (*dr*=33:1), yellow liquid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2 H), 6.90-6.88 (m, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 6.20 (s, 1 H), 4.22 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.37 -2.32 (m, 4 H), 2.08-2.05 (m, 2 H), 1.74-1.67 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.8, 157.5, 151.1, 138.7, 135.0, 126.3, 125.2, 123.8, 120.3, 112.8, 112.0, 83.5, 73.7, 63.1, 54.3, 52.1, 51.7, 31.9, 25.6, 20.5; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{23}H_{25}NO_6H$: 412.1760, found: 412.1765.

24. Synthesis of 3la

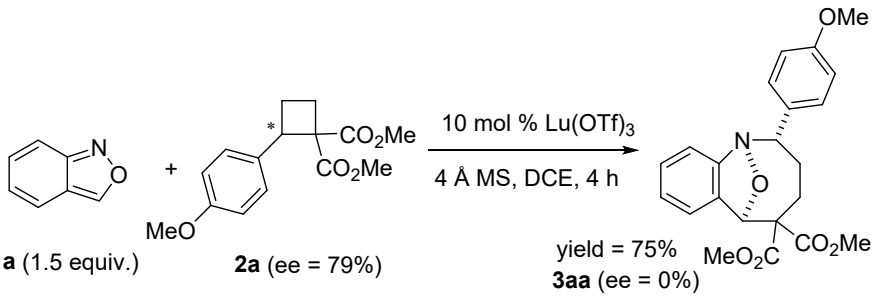


3la

The reaction of anthranil **1l** (0.225 mmol,34.6 mg), cyclobutane **2a** (0.15 mmol, 41.9 mg) and 45 mg of 4 Å M.S. and 10 mol % $Lu(OTf)_3$ in dry $ClCH_2CH_2Cl$ (1.5 ml) was carried out at rt for 15 h, eluting with (hexanes : AcOEt=7:1) to afford 51 mg (80%) of **3la**

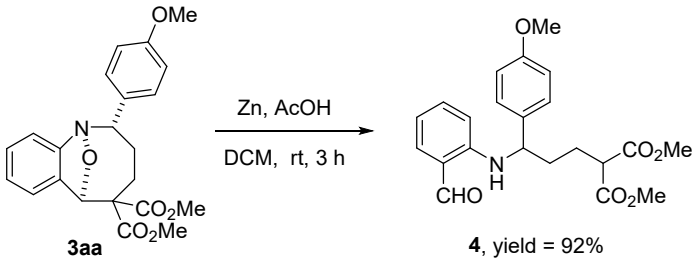
(*dr*>99:1), white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2 H), 7.27-7.25 (m, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.90-6.88 (m, 2 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 6.27 (s, 1 H), 4.53 (dd, *J* = 9.6 Hz, 6.0 Hz, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 2.47-2.41 (m, 1 H), 2.17-2.10 (m, 2 H), 1.79-1.72 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.5, 158.6, 148.9, 135.4, 131.4, 130.1, 127.5 (2C), 125.4, 120.3, 118.9, 113.8 (2C), 85.4, 71.0, 64.0, 55.3, 53.2, 52.8, 32.8, 26.7; HRMS-TOF-ES$^+$: $[M+H]^+$ calcd for $C_{22}H_{22}NO_6ClH$: 432.1214, found: 432.1214.

The [4+4] cycloaddition reaction of enantioenriched cyclobutane 2a and 1a.



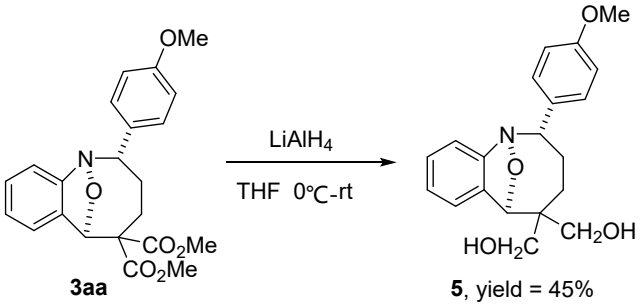
3aa, determined by HPLC, chiralcel ODH, *i*-PrOH/hexane =15/85, 1.0 mL/min, 240 nm; t_r = 14.54 min, t'_r = 35.03 min).

The transformations of cycloadduct 3aa.



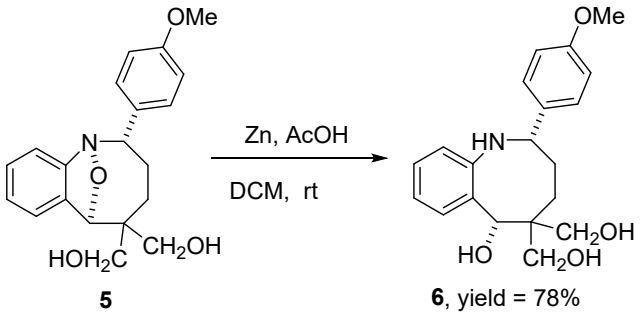
Under N_2, the cycloadduct **3aa** (40.0 mg, 0.10 mmol) and dichloromethane (2 mL) were added into an oven-dried reaction flask with stirring bar. Zinc dust (196 mg, 3.00 mmol, 30 equiv.), acetic acid (29μL, 0.5 mmol, 5.0 equiv.) were sequentially added in to the flask. Then the reaction mixture was stirred at room temperature. When **3aa** disappeared (monitored by TLC), the reaction mixture was passed over a plug of celite with 15 mL of ethyl acetate. The filtrate was removed under reduced pressure and the residue was purified by silica gel column chromatography. (petroleum ether/ethyl acetate, v/v= 10:1) to give the desired product in 92% yield (37 mg), yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.85 (s, 1 H), 8.79 (d, *J* = 6.4 Hz, 1 H), 7.46-7.44 (m, 1 H), 7.26-7.21 (m, 3 H), 6.86-6.83 (m, 2 H), 6.65 (t, *J* = 7.2 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 4.43 (dd, *J* = 13.2 Hz, 6.4 Hz, 1 H), 3.77 (s, 3 H), 3.73 (s, 3H), 3.71 (s, 3 H), 3.38 (t, *J* = 6.8 Hz, 1 H), 2.14-2.06 (m, 1 H), 1.97-1.82 (m, 3 H); ^{13}C NMR (100 MHz, CDCl3) δ 194.2, 169.43, 169.42, 158.7, 149.8, 136.5, 135.6, 134.4, 127.3, 118.6, 114.1, 112.0, 56.3, 55.2, 52.6, 52.5, 51.2, 36.0, 25.7; HRMS-TOF-ES$^+$: $[M+Na]^+$ calcd for

$C_{22}H_{25}NO_6Na$: 422.1580, found: 422.1585.



3aa **5**, yield = 45%

Under N_2, the cycloadduct **3aa** (0.47 mmol, 187.0 mg) was dissolved in THF, and cooled at 0°C, $LiAlH_4$ (2.35 mmol, 90 mg) was added into the reaction mixture. The reaction mixture was stirred at room temperature. When the cycloadduct **3aa** disappeared (monitored by TLC), the reaction mixture was quenched with H_2O (2.8 mL), 15% NaOH (2.8 mL), H_2O (8.4 mL), and then passed over a plug of celite with 50 mL of MeOH. The filtrate was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, v/v= 2:1) to give the desired product in 45% yield (80 mg), colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.33-7.28 (m, 3 H), 7.24-7.15 (m, 1 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 6.87-6.82 (m, 3 H), 5.56 (s, 1 H), 4.20 (d, *J* = 10.4 Hz, 1 H), 4.13 (dd, *J* = 10.4 Hz, 5.6 Hz, 1 H), 3.74 (s, 3 H), 3.51 (d, *J* = 10.8 Hz, 1 H), 3.35 (d, *J* = 11.2 Hz, 1H), 3.01 (brs, 1 H), 2.61 (brs, 1 H), 2.08-1.99 (m, 1 H), 1.86-1.79 (m, 1 H), 1.65 (s, 1 H), 1.22-1.14 (m, 1 H), 0.88-0.78 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 150.2, 136.6, 130.3, 128.7, 127.3, 123.7, 123.1, 113.8, 112.2, 84.0, 75.0, 67.3, 67.0, 55.3, 47.0, 32.0, 26.3; HRMS-TOF-ES$^+$:$[M+H]^+$ cacld for $C_{20}H_{23}NO_4H$: 342.1705, found: 342.1707.



5 **6**, yield = 78%

Under N_2, the cycloadduct **5** (80.0 mg, 0.21 mmol) and dichloromethane (4 mL) were added into an oven-dried reaction flask with a stirring bar. Zinc dust (412 mg, 6.30 mmol, 30 equiv.), acetic acid (61μL, 1.05 mmol, 5.0 equiv.) were sequentially added in to the flask. Then the reaction mixture was stirred at room temperature. When **5** disappeared (monitored by TLC), the reaction mixture was passed over a plug of celite with 30 mL of ethyl acetate. The filtrate was removed under reduced pressure and the residue was purified by silica gel column chromatography. (petroleum ether/ethyl acetate, v/v= 1:1) to give the desired product in 78% yield (56 mg), white solid. ^{1}H NMR (400MHz, DMSO-D_6) δ 7.35 (d, *J* = 8.4 Hz, 2 H), 7.22 (brs, 1 H), 7.13 (d, *J* = 7.2 Hz, 1 H), 7.03-6.91 (m, 4 H), 6.86 (d, *J* = 5.6 Hz, 1 H), 5.34 (d, *J* = 7.2 Hz, 1H), 4.56 (d, *J* = 5.2 Hz, 1 H), 4.47-4.41 (m, 1 H), 4.26-4.21 (m, 2 H), 3.75 (s, 3 H), 3.47-3.40 (m, 1 H),

3.35-3.30 (m, 1H), 3.25-3.18 (m, 1H), 2.89-2.85 (m, 1H), 1.56-1.45 (m, 2 H), 1.27-1.18 (m, 1 H), 1.04-0.93 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 157.9, 147.8, 137.3, 135.6, 129.1, 127.9, 127.7, 126.4, 123.0, 113.5, 74.6, 63.7, 60.4, 55.1, 47.3, 25.6, 19.1; HRMS-TOF-ES$^+$:$[M+H]^+$ cacld for $C_{20}H_{25}NO_4H$: 344.1862, found: 344.1865.