**Catalytic Enantioselective Diels Alder via a
Chiral Indium(III) Complex**

Yong-Chua Teo and Teck-Peng Loh *

Catalytic Enantioselective Diels-Alder via a Chiral Indium(III) Complex

Yong-Chua Teo^b and Teck-Peng Loh^{a*}

^a*Division of Chemistry and Biological Chemistry, Nanyang Technological University, 1
Nanyang Walk, Singapore 637616*

^b*Department of Chemistry, 3 Science Drive, National University of Singapore, Singapore
117543*

Supporting Information

Table of Contents

	Page
General Methods	S3
General Procedure for Enantioselective Diels Alder Reaction	S5
General Procedure for Enantioselective Diels Alder Reaction in Aqueous media	S6
Characterization of Diels Alder adduct	S7

General Methods

Experiments involving moisture and/or air sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen using freshly distilled solvents. Commercial grade solvents and reagents were used without further purification with the following exceptions: Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was distilled from sodium. dichloromethane, ethyl acetate were fractionally distilled. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture in *vacuo* followed by subsequent purging with nitrogen. 2-methacrolein was freshly distilled prior to usage. 1,3-cyclopentadiene was cracked at 170 °C and re-distilled. 2-bromoacrolein¹, 7-Methoxy-4-vinyl-1,2-dihydro-naphthalene² and 3-Vinyl-1H-indene was prepared according to literature procedures³.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating on a hot plate.

Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

¹(a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.

²Woski, S.A.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 5736.

³Louis, D. Q.; Alan, N. H.; Franklin, L.; Annette, L. G. *Tetrahedron* **1983**, *39*, 401.

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. Liquid samples were examined as film between NaCl salt plates.

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 500 spectrophotometer (CDCl_3 as solvent). Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.2600, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of ^1H NMR and ^{13}C NMR spectra.

Mass spectral analyses were carried out on a VG 7035 micromass mass spectrophotometer at a source temperature of 200 $^\circ\text{C}$ and at an ion current of 70 eV. Mass spectral data were reported in units of mass to charge (m/z) and % intensity.

General Procedure for Enantioselective Diels Alder Reaction

Representative procedure for enantioselective Diels-Alder reaction : Preparation of (1R,2R,4R) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10mL round-bottom flask equipped with a magnetic stirring bar was added InCl_3 (22 mg, 0.1 mmol, 0.2 equiv.). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. (*S*)-BINOL (31 mg, 0.11 mmol, 0.22 equiv.) and 4Å molecular sieve (15 mg) were added and the mixture was stirred under nitrogen at room temperature for 2 hours. Allyltributyl stannane (0.093 mL, 0.3 mmol, 0.6 equiv.) was added to the resulting mixture and stirred for 10 minutes to afford a white suspension. The pre-formed catalyst was then cooled to -40°C for 15 minutes. 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv. , added dropwise along side of the flask) were added successively and the reaction mixture stirred at -40°C for 20 h. The mixture was then quenched by addition of 5 mL of saturated NaHCO_3 and extracted with ether (10 mL X 3). The combined organic extracts was washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the diels alder adduct as a colourless solid (74% yield).

General Procedure for Asymmetric Diels Alder Reaction in Aqueous media

Representative procedure for enantioselective Diels-Alder reaction: Preparation of (1R,2R,4R) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10mL round-bottom flask equipped with a magnetic stirring bar was added InCl_3 (22 mg, 0.1 mmol, 0.2 equiv.). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. (S)-BINOL (31 mg, 0.11 mmol, 0.22 equiv.) was added and the mixture was stirred under nitrogen at room temperature for 2 hours. Allyltributyl stannane (0.093 mL, 0.3 mmol, 0.6 equiv.) was added to the resulting mixture and stirred for 10 minutes followed by 10.5 μL H_2O to afford a white suspension. The pre-formed catalyst was then cooled to -20°C for 15 minutes. 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv. , added dropwise along side of the flask) were added successively and the reaction mixture stirred at -20°C for 20 h. The mixture was then quenched by addition of 5 mL of saturated NaHCO_3 and extracted with ether (10 mL X 3). The combined organic extracts was washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the diels alder adduct as a colourless solid (64% yield).

Characterization of Diels Alder adduct

(1*R*, 2*R*, 4*R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

(98 %*ee*)

***exo* : *endo* 99 : 1**

Colorless oil (74mg, 74%); R_f = 0.65 (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 9.54 (s, 1H, *exo*), 6.45 (dd, J = 3.1, 5.6 Hz, 1H), 6.14 (dd, J = 3.1, 5.6 Hz, 1H), 3.25 (bs, 1H), 2.97 (bs, 1H), 2.65 (dd, J = 3.5, 13.6 Hz, 1H), 1.42-1.59 (m, 2H), 1.32 (d, J = 9.4 Hz, 1H).

^{13}C NMR (75.4 MHz, CDCl_3) : δ 191.9, 140.0, 133.8, 72.6, 49.6, 46.7, 42.4, 36.9.

FTIR (neat): 2978, 1722 cm^{-1} .

HRMS Calcd for $\text{C}_8\text{H}_{19}\text{BrO}$ [M^+]: 199.9837. Found:199.9834

$[\alpha]_D = +9.6^\circ$ (c = 1.37g/100mL, CH_2Cl_2)

Diastereoselectivity (*exo-endo* ratio) was determined by ^1H NMR analysis of the crude mixture: δ 9.56 (s, 1H, *exo*, major), 9.34 (s, 1H, *endo*, minor). Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^1H NMR integration (500 MHz, CDCl_3): δ 4.74 (d, 1H, minor), 4.67 (d, 1H, major), 4.61 (d, 1H, major), 4.52 (d, 1H, minor).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.⁴

⁴ Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

(1*R*, 2*S*, 4*R*)-2-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

(98 %*ee*)

***exo* : *endo* 99 : 1**

Colorless oil (48mg, 70%); R_f = 0.64 (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.68 (s, 1H), 6.28 (dd, J = 3.1, 5.6 Hz, 1H), 6.09 (dd, J = 3.1, 5.6 Hz, 1H), 2.88 (bs, 1H), 2.80 (bs, 1H), 2.24 (dd, J = 3.8, 11.9 Hz, 1H), 1.38 (m, 2H), 1.00 (s, 3H), 0.75 (bd, J = 11.8 Hz, 1H).

^{13}C NMR (75.4 MHz, CDCl_3) : δ 205.1, 138.0, 131.8, 52.3, 49.7, 45.7, 45.1, 27.6

FTIR (neat): 2918, 1726 cm^{-1} .

HRMS Calcd for $\text{C}_9\text{H}_{12}\text{O}$ [M^+]: 136.0888. Found: 136.0895.

$[\alpha]_D = +13.5^\circ$ (c = 3.10 g/100 mL, CH_2Cl_2)

Diastereoselectivity (*exo-endo* ratio) was determined by ^1H NMR analysis of the crude mixture: δ 9.68 (s, 1H, *exo*, major), 9.38 (s, 1H, *endo*, minor). Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^1H NMR integration (500 MHz, CDCl_3): δ 4.34 (d, 1H, major), 4.31 (d, 1H minor), 4.25 (d, 1H, minor), 4.22 (d, 1H, major).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.⁴

(R)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde

(96% *ee*)

Colorless oil (71mg, 70%); $R_f = 0.67$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.36 (s, 1H), 5.33 (bs, 1H), 2.79 (bd, 1H, $J = 18.1$ Hz), 2.62 (bd, 1H, $J = 18.0$ Hz), 2.09-2.28 (m, 4H), 1.67 (bs, 3H).

^{13}C NMR (75.4 MHz, CDCl_3) : δ 192.2, 134.0, 117.0, 67.0, 34.4, 30.9, 28.5, 23.1.

FTIR (neat): 2916, 1726, 1638 cm^{-1} .

HRMS Calcd for $\text{C}_8\text{H}_{11}\text{O}$ [M-Br]: 123.0810. Found: 123.0810

$[\alpha]_D = +67.7^\circ$ ($c = 1.50$ g/100 mL, CH_2Cl_2)

Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using two Daicel ADH + AD column with 1.0% i-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 51.31 min (minor), 52.57 min (major).⁵

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.⁴

⁵ The Diels-Alder adduct contains ca. 8% of its regioisomer (1-bromo-3-methylcyclohex-3-ene-1-carboxaldehyde) that cannot be separated by column chromatography.

(S)-1,4-Dimethyl-cyclohex-3-enecarbaldehyde

(90% *ee*)

Colorless oil (24mg, 35%); $R_f = 0.68$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.47 (s, 1H), 5.37 (bs, 1H), 2.32 (bd, $J = 17.1$, 1H), 1.96 (m, 2H), 1.83 (m, 2H), 1.68 (s, 3H), 1.49 (m, 1H), 1.03 (s, 3H)

^{13}C NMR (75.4 MHz, CDCl_3) : 205.0, 133.7, 118.3, 44.3, 31.8, 29.0, 26.8, 23.4, 20.7

FTIR (neat): 2924, 1725, 1633 cm^{-1} .

$[\alpha]_D = +42.0^\circ$ ($c = 3.28$ g/100mL, CH_2Cl_2)

Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^1H NMR integration (500 MHz, CDCl_3): δ 4.14 (d, 1H, major), 4.09 (d, 1H minor), 4.03 (d, 1H, minor), 3.98 (d, 1H, major).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances⁴ and by analogy with (*R*)-1-Bromo-4-methylcyclohex-3-enecarbaldehyde.

(R)-1-Bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde

(98% *ee*)

Colorless oil (80mg, 74%); $R_f = 0.67$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.34 (s, 1H), 2.74 (bd, $J = 17.4$ Hz, 1H), 2.56 (bd, $J = 17.8$ Hz, 1H), 2.08 – 2.27 (m, 4H), 1.65 (s, 3H), 1.62 (s, 3H)

^{13}C NMR (75.4 MHz, CDCl_3) : δ 192.2, 125.4, 122.2, 67.7, 40.0, 31.2, 29.9, 19.0, 18.6.

FTIR (neat): 2916, 1726, 1641 cm^{-1} .

HRMS Calcd for $\text{C}_{10}\text{H}_{13}\text{BrO}$ [M^+]: 216.0150 . Found: 216.0141.

$[\alpha]_D = +62.3^\circ$ ($c = 3.19$ g/100mL, CH_2Cl_2)

Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using Daicel AD column with 1.0% i-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 62.39 min (minor), 65.89 min (major).

The absolute configuration was assigned by analogy with (R)-1-bromo-4-methylcyclohex-3-enecarbaldehyde.

(S)-1,3,4-Trimethyl-cyclohex-3-enecarbaldehyde

(98% *ee*)

Colorless oil (48mg, 63%); $R_f = 0.68$ (4:1 hexane/ethyl acetate)

¹H NMR (300 MHz, CDCl₃) δ 9.45 (s, 1H), 2.25 (bd, *J* = 17.4 Hz, 1H), 1.97 (bs, 2H), 1.73 – 1.85 (m, 2H), 1.64 (s, 3H), 1.59 (s, 3H), 1.41 – 1.50 (m, 1H), 1.02 (s, 3H)

¹³C NMR (75.4 MHz, CDCl₃) : δ 206.2, 125.2, 123.1, 45.3, 38.0, 29.3, 28.5, 20.7, 19.2, 18.8.

FTIR (neat): 2918, 1726 cm^{-1} .

HRMS Calcd for C₁₀H₁₆O [M⁺]: 152.1201. Found: 152.1198.

$$[\alpha]_{\text{D}} = +48.0^{\circ} \text{ (c = 4.60 g/100mL, CH}_2\text{Cl}_2\text{)}$$

Enantioselectivity was determined by reduction with NaBH₄ to the corresponding alcohol, conversion to the (R)-MTPA ester derivative and ¹H NMR integration (500 MHz, CDCl₃): δ 4.12 (d, 1H, major), 4.08 (d, 1H minor), 4.01 (d, 1H, minor), 3.98 (d, 1H, major).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methylcyclohex-3-enecarbaldehyde.

(2S)-2-Bromo-2,3,9a-tetrahydro-1H-fluorene-2-carbaldehyde

(98% *ee*)

Light yellow solid (100mg, 72%); $R_f = 0.60$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.54 (s, 1H), 7.43 – 7.46 (m, 1H), 7.22 – 7. (m, 3H), 5.94 (dd, $J = 7.0, 3.5$, 1H), 3.35 – 3.49 (m, 1H), 3.14 – 3.24 (m, 2H), 2.87 (bd, $J = 17.8$, 1H), 2.72 (dd, $J = 15.0, 9.0$, 1H), 2.55 (ddd, $J = 13.6, 4.9, 1.1$, 1H), 1.66 (dd, $J = 13.2, 11.2$, 1H)

^{13}C NMR (75.4 MHz, CDCl_3) : δ 192.1, 144.3, 143.6, 140.0, 128.2, 126.9, 125.2, 120.5, 111.0, 68.9, 38.2, 36.8, 35.4, 34.5

FTIR (neat): 2843, 1720, 1420, 752 cm^{-1} .

HRMS Calcd for $\text{C}_{14}\text{H}_{13}\text{BrO}$ [M^+]: 276.0150 Found: 276.0150.

$[\alpha]_D = +165.0^\circ$ ($c = 2.10$ g/100mL, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 20.28 min (major), 21.12 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2*R*)-2-Methyl-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde

(98% *ee*)

Colorless solid (75mg, 71%); $R_f = 0.65$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.54 (s, 1H), 7.39 – 7.42 (m, 1H), 7.18 – 7.27 (m, 3H), 5.97 (dd, $J = 7.3, 3.5$, 1H), 3.14 (dd, $J = 15.0, 8.4$, 1H), 2.93 – 2.99 (m, 1H), 2.53 – 2.64 (m, 2H), 1.91 – 2.03 (m, 2H), 1.49 – 1.57 (m, 1H), 1.20 (s, 3H)

^{13}C NMR (75.4 MHz, CDCl_3) : δ 205.2, 144.2, 143.1, 140.6, 127.7, 126.7, 125.1, 120.1, 113.8, 45.52, 37.6, 36.7, 33.5, 31.0, 19.1

FTIR (neat): 2923, 1712, 1454, 744 cm^{-1} .

HRMS Calcd for $\text{C}_{15}\text{H}_{16}\text{O}$ [M^+]:212.1201. Found:212.1200.

$[\alpha]_D = +50.5^\circ$ ($c = 1.0$ g/100mL, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ASH + ADH column with 1.0% i-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 11.03 min (major), 11.40 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2S)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde

(94% *ee*)

Light yellow solid (123mg, 77%); $R_f = 0.51$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.52 (s, 1H), 7.56 (d, $J = 8.7$, 1H), 6.75 (dd, $J = 8.7$, 2.8), 6.63 (d, $J = 2.4$, 1H), 6.09 – 6.11 (m, 1H), 3.80 (s, 3H), 2.93 – 3.10 (m, 2H), 2.71 – 2.90 (m, 3H), 2.02 – 2.37 (m, 1H), 2.02 – 2.06 (m, 1H), 1.52 – 1.68 (m, 2H)

^{13}C NMR (75.4 MHz, CDCl_3) : δ 192.6, 158.9, 137.9, 135.5, 126.3, 125.2, 113.3, 112.9, 111.9, 68.2, 55.3, 37.2, 34.7, 33.9, 30.2, 30.1

FTIR (neat): 2928, 1717, 1494, 1234, 810 cm^{-1} .

HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{BrO}_2$ [M^+]: 320.0412. Found:320.0408

$[\alpha]_D = -58.2^\circ$ ($c = 2.0\text{g}/100\text{mL}$, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 10.65 min (major), 12.49 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2R)-2-Methyl-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde

(97% *ee*)

Colorless solid (96mg, 75%); $R_f = 0.57$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) δ 9.54 (s, 1H), 7.53 (d, $J = 8.7$, 1H), 6.74 (dd, $J = 8.7$, 2.4), 6.62 (bd, $J = 2.4$, 1H), 6.11 - 6.13 (m, 1H), 3.79 (s, 3H), 2.80 - 3.00 (m, 2H), 2.57 (bd, $J = 18.1$, 1H), 2.33 - 2.45 (m, 1H), 1.92 - 2.00 (m, 2H), 1.68 - 1.75 (m, 1H), 1.39 - 1.58 (m, 2H), 1.15 (s, 3H)

^{13}C NMR (75.4 MHz, CDCl_3) : δ 205.8, 158.6, 137.7, 134.8, 126.9, 124.8, 114.4, 113.3, 112.8, 55.2, 44.5, 35.5, 31.8, 31.7, 30.8, 30.2, 18.0

FTIR (neat): 2927, 1721, 1499, 821 cm^{-1} .

HRMS Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2$ [M^+]: 256.1463. Found: 256.1463.

$[\alpha]_D = -117.0$ ($c = 1.36$ g/100mL, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 2.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 7.38 min (major), 8.51 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.