Catalytic enantioselective Diels-Alder reaction in
ionic liquid via a recyclable chiral In(III) complex

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Supporting Information

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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. Hexane, 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-Bromoacrolein,¹ 7-methoxy-4-vinyl-1,2-dihydro-naphthalene² was prepared according to literature procedures.³

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.

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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); bs (broad singlet); d (doublet); bd (broad doublet); t (triplet); q (quartet); dd (doublets of doublet); or m (multiplets). The number of protons (*n*) for a given resonance is indicated by *n*H. 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 °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 in ionic liquid

Representative procedure for enantioselective Diels-Alder reaction : Preparation of (1*R*, 2*R*, 4*R*) -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 InCl₃ (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 followed by addition of 1 mL of hmim[PF₆⁻] to the pre-formed catalyst. The organic solvent was removed *in vacuo* and subsequent dropwise addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv.) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) along side of the flask were carried out. The reaction mixture was stirred at room temperature for 20 h. The mixture was extracted with ether (10 mL X 3). The combined organic extracts was washed with brine, dried over anhydrous MgSO₄, 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 (92% yield).

Procedure for Asymmetric Diels-Alder Reaction in Ionic Liquid (recyclability)

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

To an oven dried 10 mL 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 followed by addition of 1 mL of $\text{hmim}[\text{PF}_6^-]$ to the pre-formed catalyst. The organic solvent was removed *in vacuo* and subsequent dropwise addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv.) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) along side of the flask were carried out. The reaction mixture was stirred at room temperature for 20 h. The rubber septum was removed and the mixture was extracted with hexane (10 mL X 5). The round-bottom flask was resealed with a rubber septum and anhydrous THF (2 mL X 2) was added to the $\text{hmim}[\text{PF}_6^-]$ containing chiral In(III) complex mixture for the removal of residual hexane and moisture *in vacuo*. The mixture was purge with nitrogen prior to addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv.) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) for subsequent cycles of Diels-Alder reaction. 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 flash column chromatography to afford the Diels-Alder adduct as a colourless solid.

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* 97 : 3**

Colorless oil (92 mg, 92%) ; 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 $\text{C}_8\text{H}_9\text{BrO}$ $[\text{M}]^+$: 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

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

Product 2 ^{13}C

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

(98 %*ee*)

***exo* : *endo* 97 : 3**

Colorless oil (60mg, 89%) ; 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), 1.38-1.37 (m, 2H), 1.00 (s, 3H), 0.75 (bd, J = 11.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3) : δ 205.7, 139.5, 133.0, 53.8, 48.3, 47.5, 43.1, 34.5, 19.9

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

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

Product 1 ¹H

ma25 4041.666 pure

Product 1 ¹³C

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

(96% *ee*)

Colorless oil (55 mg, 90%) ; 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 Daicel Chiral ADH and Daicel Chiral AD column in series with 1.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 88.612 min (minor), 92.248 min (major).⁵

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

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⁵ The Diels-Alder adduct contains ca. 16% of its regioisomer (1-bromo-3-methylcyclohex-3-ene-1-carboxaldehyde) that cannot be separated by column chromatography.

Product 5 ¹H

Product 5 ¹³C

ma224039.666 carbon

Product 5 HPLC spectrum

#	Time	Area	Height	Width	Area%	Symmetry
1	88.612	796.7	7.3	1.8119	1.607	1.8
2	92.248	48780.7	176.6	4.6043	98.393	0.457

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

(88% ee)

Colorless oil (54mg, 78%) ; $R_f = 0.68$ (4:1 hexane/ethyl acetate)

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

^{13}C NMR (100 MHz, CDCl_3) : 206.1, 133.7, 118.3, 44.3, 31.7, 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-methyl-cyclohex-3-enecarbaldehyde.

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⁵ The Diels-Alder adduct contains ca. 23% of its regioisomer that cannot be separated by column chromatography.

Product 4 ^1H

Product 4 ¹³C

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

(94% *ee*)

Colorless oil (97 mg, 90%); $R_f = 0.67$ (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 $\text{C}_{19}\text{H}_{13}\text{BrO}$ $[\text{M}]^+$: 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 Chiral AD column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 89.943 min (minor), 100.579 min (major).

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

Product 7 ¹H

ap13 4017.666 pure proton

Product 7 ¹³C

ap13 4017 666 carbon

Product 7 HPLC spectrum

#	Time	Area	Height	Width	Area%
1	89.943	9100.7	81.2	1.867	2.831
2	100.575	312404.7	1087.7	4.787	97.169

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

(97% ee)

Colorless oil (67 mg, 88%); $R_f = 0.68$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3) 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)

^{13}C NMR (75.4 MHz, CDCl_3) : 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 $\text{C}_{10}\text{H}_{16}\text{O}$ $[\text{M}]^+$: 152.1201. Found: 152.1198.

$[\alpha]_D = +48.0^\circ$ ($c = 4.60$ 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 4.12 (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-methyl-cyclohex-3-enecarbaldehyde.

Product 6 ¹H

apoi 050 carbon. 666

Product 6 ¹³C

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

(92% *ee*)

Light yellow solid (142mg, 89%); $R_f = 0.51$ (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, 1H), 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 $\text{C}_{16}\text{H}_{17}\text{BrO}_2$ $[\text{M}]^+$: 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 Daicel Chiral ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 10.650 min (major), 12.492 min (minor).

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

Product 8 ¹H

my29.4105 pure

Product 8 ^{13}C

Product 8 HPLC spectrum

Info :
da, ad-H, all, chiral

#	Name	RT	Area[$\mu V \cdot Sec$]	%Area Corr.	Area
1		10.650	8062546.524	97.27	8062546.52
2		12.492	1.724	0.00	225929.25

Total Area of Peak = 8288475.774 [$\mu V \cdot Sec$]