Supporting Information

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The First Organocatalytic Enantioselective Inverse Electron-Demand Hetero-Diels-Alder Reaction

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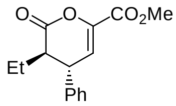
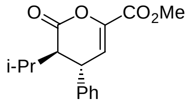
General Methods. The ^{1}H and ^{13}C NMR spectra were recordered at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ (δ=7.26) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ=77.0) for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. Flash chromatography (FC) was carried out using silica gel 60 (230-400 mesh). The enantiomeric excess (ee) of the products were determined by HPLC using Chiracel OD or Chiralpack AD or AS columns with *i*-PrOH/hexane as eluent or by chiral GC using a G-TA column. HPLC and GC traces were compared to racemic samples prepared with pyrrolidine as the catalyst.

Materials Amines **1a-c** are commercially available. Amines **1d**,**e** were prepared according to a literature procedure.[1] Aldehydes **3a-c** are commercially available. Enones **4a-b** were prepared according to literature procedures.[2] Enone **4c** was prepared by a Wittig reaction of ethyl-triphenylphosphoranylpyruvat[3] and acetaldehyde.

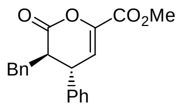
General Procedure for Catalytic Enantioselective Inverse Electron-Demand Hetero-Diels-Alder Reaction. The aldehyde (0.50 mmol) and the enone (1.00 mmol) were dissolved in 0.5 mL of CH_2Cl_2 and cooled to –15°C. The catalyst (0.05 mmol) was added followed by the addition of 50 mg of silica and the mixture was allowed to warm to room temperature while stirring over night. The equilibrium mixture of **6** and **7** was isolated by FC (silica, gradient CH_2Cl_2 to 15% Et_2O/CH_2Cl_2). Oxidation of the mixture of **6** and **7** was performed in CH_2Cl_2 by adding 1 equivalent of PCC at room temperature. After 1 h, another equivalent of PCC was added and after 2 h the lactone **8** was isolated in 65% yield by FC with CH_2Cl_2 as the eluent.



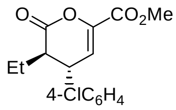
5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8aa). The ee was determined by HPLC using a Chiralpak OD column (95/5 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{minor} = 16.9 min; τ_{major} = 21.4 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +115° (*c* = 10 mg/mL, CH_2Cl_2, 84% ee). ^{1}H NMR δ 7.27 (m, 3H), 7.09 (d, *J* = 7.6, 2H), 6.46 (d, *J* = 4.5, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 4.5, 7.5, 1H), 2.64 (dt, *J* = 5.3, 7.5, 1H), 1.62 (m, 2H), 0.95 (t, *J* = 7.3, 3H). ^{13}C NMR δ 168.0, 160.7, 141.3, 139.5, 129.2 (2C), 127.8, 127.3 (2C), 117.6, 52.6, 46.9, 42.2, 22.5, 11.0. HRMS $[M+Na]^+$ $C_{15}H_{16}NaO_4$ calculated 283.0946 found 283.0948.



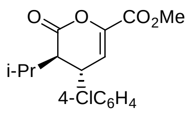
5-Isopropyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8ba). The ee was determined by HPLC using a Chiralpak OD column (98/2 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{minor} = 17.0 min; τ_{major} = 21.7 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +215° (*c* = 10 mg/mL, CH_2Cl_2, 90% ee). ^{1}H NMR δ 7.30-7.19 (m, 5H), 7.06 (d, *J* = 8.2, 2H), 6.49 (dd, *J* = 1.1, 5.9, 1H), 3.80 (s, 3H), 3.74 (dd, *J* = 3.6, 5.9, 1H), 2.49 (ddd, *J* = 1.1, 3.6, 7.7, 1H), 1.89 (octet, *J* = 6.9, 1H), 1.06 (d, *J* = 6.9, 3H), 0.97 (d, *J* = 6.9, 3H). ^{13}C NMR δ 167.2, 160.8, 141.7, 139.6, 129.3 (2C), 127.8, 127.1 (2C), 116.1, 53.2, 52.6, 41.1, 29.1, 20.9, 19.8. HRMS $[M+Na]^+$ $C_{16}H_{18}NaO_4$ calculated 297.1103 found 297.1101.



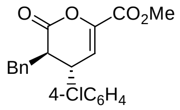
5-Benzyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8ca). The ee was determined by HPLC using a Chiralpak OD column (80/20 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{major} = 13.4 min; τ_{minor} = 20.4 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +144° (*c* = 10 mg/mL, CH_2Cl_2, 86% ee). ^{1}H NMR δ 7.29 (m, 6H), 7.15 (d, *J* = 7.8, 2H), 7.04 (d, *J* = 7.8, 2H), 6.53 (d, *J* = 5.1, 1H), 3.88 (s, 3H), 3.61 (t, *J* = 5.2, 1H), 3.09 (m, 2H), 2.90 (dd, *J* = 7.0, 13.2, 1H). ^{13}C NMR δ 167.9, 160.7, 141.6, 139.1, 137.2, 129.2 (2C), 129.1 (2C), 128.7 (2C), 127.9, 127.3 (2C), 127.0, 116.5, 52.7, 47.6, 41.3, 35.5. HRMS $[M+Na]^+$ $C_{20}H_{18}NaO_4$ calculated 345.1103 found 345.1101.



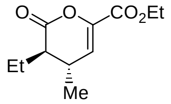
5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8ab). The ee was determined by HPLC using a Chiralpack AD column (90/10 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{minor} = 10.9 min; τ_{major} = 12.6 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +163° (*c* = 13 mg/mL, CH_2Cl_2, 85% ee). ^{1}H NMR δ 7.26 (d, *J* = 8.6, 2H), 7.09 (d, *J* = 8.6, 2H), 6.42 (d, *J* = 4.6, 1H), 3.80 (s, 3H), 3.61 (dd, *J* = 4.6, 7.4, 1H), 2.59 (dt, *J* = 4.9, 7.4, 1H), 1.62 (m, 2H), 0.95 (t, *J* = 7.3, 3H). ^{13}C NMR δ 167.7, 160.6, 141.6, 138.0, 133.7, 129.4 (2C), 128.6 (2C), 116.8, 52.7, 46.9, 41.6, 22.5, 11.0. HRMS $[M+Na]^+$ $C_{15}H_{15}ClNaO_4$ calculated 317.0557 found 317.0558.



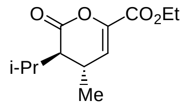
5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8bb). The ee was determined by HPLC using a Chiralpack AS column (93/7 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{minor} = 11.8 min; τ_{major} = 12.8 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +203° (*c* = 17 mg/mL, CH_2Cl_2, 90% ee). ^{1}H NMR δ 7.29 (d, *J* = 8.5, 2H), 7.05 (d, *J* = 8.5, 2H), 6.51 (d, *J* = 5.8, 1H), 3.86 (s, 3H), 3.78 (dd, *J* = 3.7, 5.8, 1H), 2.49 (dd, *J* = 3.7, 7.7, 1H), 1.93 (m, 1H), 1.11 (d, *J* = 6.7, 3H), 1.02 (d, *J* = 6.7, 3H). ^{13}C NMR δ 166.9, 160.7, 142.1, 138.0, 129.4 (2C), 128.4 (2C), 115.4, 53.3, 52.7, 40.4, 29.0, 20.8, 19.8. HRMS $[M+Na]^+$ $C_{16}H_{17}ClNaO_4$ calculated 331.0713 found 331.0705.



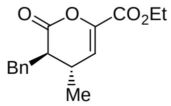
5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8cb). The ee was determined by HPLC using a Chiralpak AD column (90/10 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{major} = 12.5 min; τ_{minor} = 14.8 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +133° (*c* = 14 mg/mL, CH_2Cl_2, 80% ee). ^{1}H NMR δ 7.28 (m, 5H), 7.14 (d, *J* = 8.3, 2H), 6.95 (d, *J* = 8.3, 2H), 6.48 (d, *J* = 5.3, 1H), 3.87 (s, 3H), 3.59 (t, *J* = 5.3, 1H), 3.07 (m, 1H), 3.06 (dd, *J* = 6.0, 15.3 H), 2.89 (dd, *J* = 9.5, 15.3 H). ^{13}C NMR δ 167.5, 160.5, 141.8, 137.5, 136.9, 133.7, 129.4 (2C), 129.0 (2C), 128.7 (2C), 128.6 (2C), 127.1, 115.7, 52.7, 47.5, 40.5, 35.5. HRMS $[M+Na]^+$ $C_{20}H_{17}ClNaO_4$ calculated 379.0713 found 379.0724.



5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8ac). The ee was determined by GC using a G-TA column (τ_{major} = 23.7 min; τ_{minor} = 24.3 min). A diastereomeric ratio of dr = 45:1 was observed by GC analysis. $[\alpha]^{rt}_{D}$= +110° (*c* = 10 mg/mL, CH_2Cl_2, 86% ee). ^{1}H NMR δ 6.40 (d, *J* = 4.9, 1H), 4.29 (q, *J* = 7.2, 2H), 2.56 (m, 1H), 2.33 (m, 1H), 1.69 (m, 2H), 1.33 (d, *J* = 7.2, 2H), 1.16 (d, *J* = 7.3, 2H), 0.99 (t, *J* = 7.4, 2H). ^{13}C NMR δ 168.9, 160.5, 140.8, 119.3, 61.8, 46.7, 30.5, 22.1, 19.1, 14.1, 10.9. HRMS $[M+Na]^+$ $C_{11}H_{16}NaO_4$ calculated 235.0946 found 235.0954.



5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8bc). The ee was determined by GC using a G-TA column (τ_{major} = 24.8 min; τ_{minor} = 25.7 min). Only one diastereomer was observed by GC analysis. $[\alpha]^{rt}_{D}$= +165° (*c* = 15 mg/mL, CH_2Cl_2, 94% ee). ^{1}H NMR δ 6.44 (dd, *J* = 1.2, 6.2, 1H), 4.28 (dq, *J* = 2.1, 7.1 2H), 2.66 (m, 1H), 2.19 (ddd, *J* = 1.2, 2.6, 8.7, 1H), 1.84 (double septet, *J* = 6.6, 8.7, 1H), 1.32 (t, *J* =7.1, 3H), 0.99 (d, *J* = 6.6, 6H). ^{13}C NMR δ 168.2, 160.4, 141.1, 118.4, 61.7, 53.0, 29.5, 28.2, 20.8, 20.4, 19.7, 14.1. HRMS $[M+Na]^+$ $C_{12}H_{18}NaO_4$ calculated 249.1103 found 249.1096.



5-Ethyl-6-oxo-4-phenyl-5,6-dihydro-4*H*-pyran-2-carboxylic acid methyl ester (8cc). The ee was determined by HPLC using a Chiralpak OD column (99/1 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{major} = 31.2 min; τ_{minor} = 35.7 min). Only one diastereomer was observed by HPLC analysis. $[\alpha]^{rt}_{D}$= +72° (*c* = 17 mg/mL, CH_2Cl_2, 89% ee). ^{1}H NMR δ 7.33-7.17 (m, 5H), 6.42 (d, *J* = 5.3, 1H), 4.31 (q, *J* = 7.2, 2H), 3.02 (dd, *J* = 6.1, 13.8, 1H), 2.88 (dd, *J* = 8.0, 13.8, 1H), 2.73 (m, 1H), 2.45 (m, 1H), 1.35 (t, *J* = 7.2, 3H), 1.11 (d, *J* = 7.2, 3H). ^{13}C NMR δ 168.6, 160.3, 140.9, 137.2, 129.1 (2C), 128.7 (2C), 126.9, 118.5, 61.8, 47.2, 35.1, 29.6, 19.2, 14.1. HRMS $[M+Na]^+$ $C_{16}H_{18}NaO_4$ calculated 297.1103 found 297.1110.

References:

[1] D. O'Hagan, M. Tavasli, *Tetrahedron Asymmetry*, **1999**, *10*, 1189.
[2] H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487.
[3] T. K. M. Shing, *Tetrahedron Lett.* **1992**, *33*, 1307.