Chem. Eur. J. **2002**

Supporting Information

for

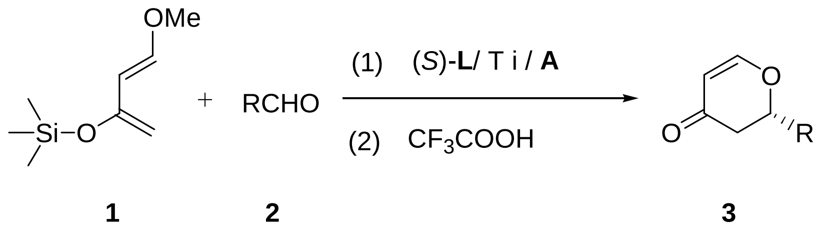
Dramatically Synergetic Effect of Carboxylic Acid Additive on Tridentate Titanium Catalyzed Enantioselective Hetero-Diels-Alder Reaction: Additive Acceleration and Nonlinear Effect

Yu Yuan, Jiang Long, Jie Sun, and Kuiling Ding*

[*] Prof. Dr. K. Ding, Dr. Jiang Long, Mr. Y. Yuan, Mr. Jie Sun
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Road
Shanghai 200032, P. R. China
Fax: (+86) 21-6416-6128
E-mail: kding@pub.sioc.ac.cn

General Considerations

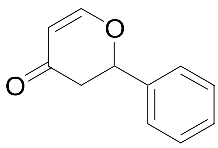
^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 at 25°C. Chemical shifts were expressed in ppm with TMS as an internal standard (δ = 0 ppm) for ^{1}H NMR. Liquid chromatographic analyses were conducted on a JASCO 1580 system. EI Mass spectra were obtained on a HP5989A spectrometer. HRMS was determined on a Kratos Concept instrument. Elemental analysis was performed with an Elemental VARIO EL apparatus. All the experiments which are sensitive to moisture or air were carried out under argon atmosphere using standard Schlenk techniques. Commercial reagents were used as received without further purification unless otherwise noted. Toluene was freshly distilled from sodium benzophenone ketyl and methanol from magnesium.



General Procedure for Catalytic Enantioselctive Hetero-Diels-Alder Reaction : A mixture of (*S*)-Schiff Base (0.05 mmol), 0.5 M Ti(O*i*Pr)$_4$ in CH_2Cl_2 (50 μl, 0.05 mmol) and activated power 4A MS (30 mg) in toluene (1 ml) was stirred for 2 h at 50°C. The red mixture was cooled to room temperature and the carboxylic acid (0.025 mmol), aldehyde (0.25 mmol) and Danishefsky's diene (60 μl, 0.3 mmol) were added sequentially. After 20 h, the solution was treated with 10 drops TFA. After the mixture was stirred for 5 min, saturated $NaHCO_3$ (3 ml) was added. The mixture was stirred for further 5 min and fitered through a plug of Celite. The Organic layer was separated and the aqueous layer was extracted with ethyl ester (5×5 ml), the combinated organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography to give the cycloadduct.

Characterization of Cycloadducts 3a-3k

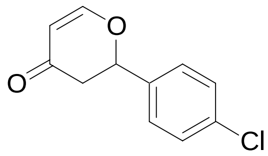
All the aldehydes were purchased from commercial suppliers. 1-Methoxy-3-(trimethyl-silyloxyl)buta-1,3-diene was prepared according to literature procedure.[1]



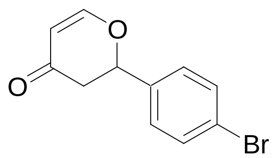
(*S*)-2-Phenyl-2,3-dihydro-*4H*-pyran-4-one (3a).[2] IR (liquid film) ν_{max} 3064, 1676, 1596, 1402, 1272, 1228, 1210, 1040, 990, 934, 864, 826, 796, 760, 732, 720, 640, 612 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.49 (d, J = 5.98 Hz, 1H), 7.47-7.39 (m, 5H), 5.54 (dd, J = 5.98, 0.98 Hz, 1H), 5.44 (dd, J = 14.18, 3.46 Hz, 1H), 2.97-2.87 (m, 1H), 2.70-2.63 (m, 1H). EIMS *m/z* (relative intensity): 174 (M^+, 0.95), 156 (11.59), 145 (13.20), 131 (5.34), 115 (2.59), 104 (100.00), 91 (3.89), 77 (22.89), 69(10.24).

Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane :

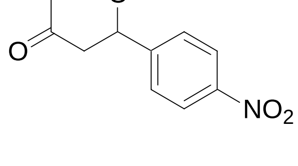
isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 11.450 min (*S*), t_{R2} = 13.467 min (*R*).



2-(4-Chlorophenyl)-2,3-dihydro-*4H*-pyran-4-one (3b).[3] IR (liquid film) ν_{max} 3070, 2970, 2906, 2632, 2076, 1907, 1683, 1597, 1496, 1402, 1272, 1228, 1209, 1091, 1040, 934, 834, 822 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.58 (d, J = 6.02 Hz, 1H), 7.52-7.44 (m, 4H), 5.65 (dd, J = 6.07, 1.03 Hz, 1H), 5.55 (dd, J = 14.24, 3.57 Hz, 1H), 3.02-2.92 (m, 1H), 2.79-2.72 (m, 1H). EIMS *m/z* (relative intensity): 208 (M^+, 2.52), 190 (14.15), 179 (7.91), 138 (100.00), 103 (60.19), 77 (14.69), 69(10.62).
Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 12.525 min (major), t_{R2} = 15.308 min (minor).

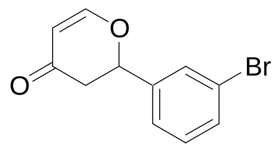


2-(4-Bromophenyl)-2,3-dihydro-*4H*-pyran-4-one (3c). IR (liquid film) ν_{max} 3087, 2970, 2893, 1922, 1683, 1668, 1593, 1487, 1401, 1270, 1227, 1209, 1038, 933, 834, 814 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.58-7.57 (m, 2H), 7.46 (dd, J = 5.87, 0.49 Hz, 1H), 7.31-7.27 (m, 2H), 5.53 (dd, J = 6.11, 1.22 Hz, 1H), 5.43 (dd, J = 14.17, 3.42 Hz, 1H), 2.91-2.81 (m, 1H), 2.68-2.61 (m, 1H). EIMS *m/z* (relative intensity): 254 ($[M+2]^+$, 5.13), 252 (M^+, 5.42), 184 (96.52), 182 (100.00), 103(61.81), 77(64.91), 69(31.27). HRMS (EI) caled for $C_{11}H_9BrO_2$ (M^+): 251.9786. Found: 251.9780. Anal. calcd for $C_{11}H_9BrO_2$: C 52.20, H 3.58%. Found: C 52.47, H 3.82%.
Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 13.708 min (major), t_{R2} = 17.725 min (minor).



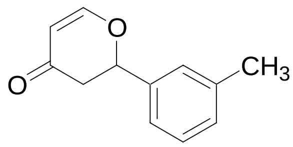
2-(4-Nitrophenyl)-2,3-dihydro-*4H*-pyran-4-one (3d).[4] IR (KBr) ν_{max} 3071, 2962, 2629, 2460, 1930, 1679, 1593, 1523, 1409, 1353, 1263, 1228, 1037, 934, 857, 849 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.31 (d, J = 11.61 Hz, 2H), 7.61 (d, J = 11.00 Hz, 2H), 7.51 (d, J = 6.11 Hz, 1H), 5.59-5.57 (m, 1H), 5.53-5.52 (d, J = 4.28 Hz, 1H), 2.89-2.68 (m, 2H). EIMS *m/z* (relative intensity): 219 (M^+, 9.21), 201 (21.16), 190 (7.75), 173 (2.07), 149 (100.00), 119 (51.05), 103 (47.68) 91 (50.93), 77 (81.13), 69(22.28).

Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 25.725 min (major), t_{R2} = 36.783 min (minor).



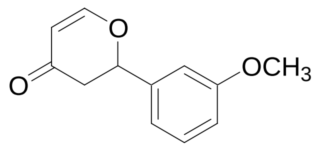
2-(3-Bromophenyl)-2,3-dihydro-*4H*-pyran-4-one (3e). IR (liquid film) ν_{max} 3065, 2970, 2901, 2629, 2358, 1683, 1592, 1569, 1403, 1270, 1226, 1038, 997, 877, 834 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.54-7.47 (m, 2H), 7.33-7.27 (m, 2H), 5.55 (dd, J=6.00, 1.23 Hz, 1H), 5.42 (dd, J=14.23, 3.63 Hz, 1H), 2.91-2.80 (m, 1H), 2.69-2.62 (m, 1H). EIMS *m/z* (relative intensity): 254 ($[M+2]^+$, 10.30), 252 (M^+, 10.64), 184 (93.87), 182 (100.00), 144(11.13), 103(70.63), 77(46.24), 69(8.07). HRMS (EI) caled for $C_{11}H_9BrO_2$ (M^+): 251.9786. Found: 251.9757. Anal. calcd for $C_{11}H_9BrO_2$: C 52.20, H 3.58%. Found: C 52.36, H 3.93%.

Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 12.817 min (major), t_{R2} = 16.700 min (minor).



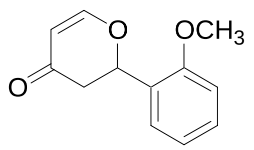
2-(3-Methylphenyl)-2,3-dihydro-*4H*-pyran-4-one (3f).[5] IR (liquid film) ν_{max} 3055, 2968, 2920, 2626, 1683, 1591, 1402, 1271, 1221, 1039, 990, 899, 841 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.48 (d, J = 5.98 Hz, 1H), 7.29-7.16 (m, 4H), 5.53 (dd, J = 6.00, 0.94 Hz, 1H), 5.42 (dd, J = 14.40, 3.60 Hz, 1H), 2.97-2.86 (m, 1H), 2.68-2.61 (m, 1H), 2.39 (s, 3H). EIMS *m/z* (relative intensity): 188 (M^+, 1.36), 170 (9.30), 159 (16.21), 145 (3.08), 131 (4.28), 117 (100.00), 91 (25.64), 77 (6.84), 69(11.91).

Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 10.150 min (major), t_{R2} = 12.150 min (minor).



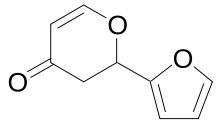
2-(3-Methoxyphenyl)-2,3-dihydro-*4H*-pyran-4-one (3g). IR (liquid film) ν_{max} 3063, 2964, 2838, 1719, 1677, 1592, 1491, 1270, 1224, 1041, 992, 877, 844 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.49 (d, J = 5.97 Hz, 1H), 7.34 (t, J = 7.81 Hz, 1H), 6.99-6.90 (m, 3H), 5.54 (dd, J = 6.10, 1.15 Hz, 1H), 5.42 (dd, J = 14.36, 3.46 Hz, 1H), 3.83 (s, 3H), 2.95-2.85 (m, 1H), 2.70-2.62 (m, 1H). EIMS *m/z* (relative intensity): 204 (M^+, 20.33), 186 (11.52), 175 (11.58), 134 (100.00), 104 (16.78), 91 (24.43), 77(10.80), 69(5.26). HRMS (EI) caled for $C_{12}H_{12}O_3$ (M^+): 204.0786. Found: 204.0753.

Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 18.025 min (major), t_{R2} = 24.408 min (minor).

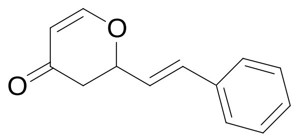


2-(4-Meyhoxyphenyl)-2,3-dihydro-*4H*-pyran-4-one (3h).[4] IR (liquid film) ν_{max} 3073, 2966, 2627, 1720, 1681, 1589, 1497, 1274, 1111, 1041, 991, 934, 871 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.53-7.47 (m, 2H), 7.37 (t, J = 7.90Hz, 1H), 7.03 (t, J = 7.55Hz, 1H), 6.91 (d, J = 8.31Hz, 1H), 5.81 (dd, J = 11.44, 6.41Hz, 1H), 5.51 (d, J = 6.00Hz, 1H), 3.84 (s, 3H), 2.77-2.73 (m, 2H). EIMS *m/z* (relative intensity): 204 (M^+, 10.59), 186 (10.58), 175 (15.04), 134 (49.42), 119 (84.43), 105 (13.43), 91 (100.00), 77 (15.78), 69(10.71).

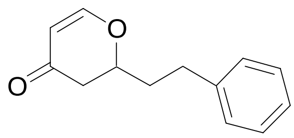
Enantiomeric excess was determined by HPLC on Chiralpak AD column, hexane : isopropanol = 99.5 : 0.5, flow rate = 1.0 mL/min, t_{R1} = 32.200 min (minor), t_{R2} = 39.100 min (major).



2-(2-Furyl)-2,3-dihydro-*4H*-pyran-4-one (3i).[6] IR (liquid film) ν_{max} 3136, 3057, 2974, 2627, 1662, 1595, 1405, 1286, 1205, 1033, 997, 962, 880, 842 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.49 (d, J = 1.47 Hz, 1H), 7.39 (d, J = 6.06 Hz, 1H), 6.47-6.41 (m, 2H), 5.52-5.46 (m, 2H), 3.15-3.05 (m, 1H), 2.77-2.70 (m, 1H). EIMS *m/z* (relative intensity): 164 (M^+, 12.96), 146 (2.63), 136 (1.70), 94 (100.00), 69 (7.60), 66 (31.44).
Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 95 : 5, flow rate = 0.7 mL/min, t_{R1} = 18.742 min (minor), t_{R2} = 20.217 min (major).



2-(E-Styryl)-2,3-dihydro-*4H*-pyran-4-one (3j).[6] IR (liquid film) ν_{max} 3027, 2926, 1719, 1676, 1592, 1449, 1406, 1267, 1217, 1038, 967, 899, 820 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.43-7.27 (m, 6H), δ 6.72 (d, J = 15.89 Hz, 1H), 6.31 (dd, J = 15.91, 6.56 Hz, 1H), 5.49 (d, J = 5.74 Hz, 1H), 5.11-5.04 (m, 1H), 2.79-2.58 (m, 2H). EIMS *m/z* (relative intensity): 200 (M^+, 24.12), 129 (100.00), 115 (53.23), 102 (10.22), 91 (13.62), 77 (18.77), 69(22.68).
Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 19.992 min (major), t_{R2} = 41.933 min (minor).

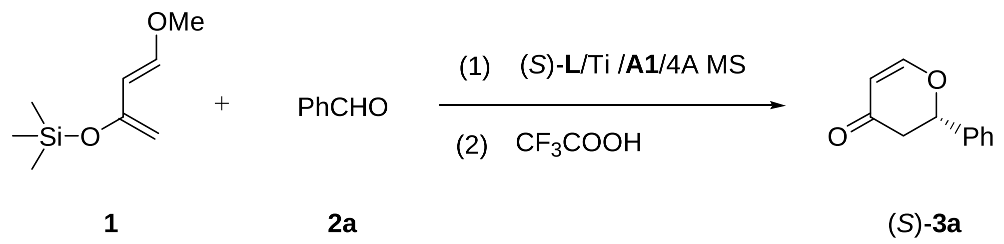


(*S*)-2-Phenylethyl-2,3-dihydro-*4H*-pyran-4-one (3k).[1] IR (liquid film) ν_{max} 3063, 2930, 2866, 1720, 1676, 1595, 1496, 1455, 1407, 1270, 1227, 1197, 1045, 943, 888, 832 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.39 (d, J = 6.11Hz, 1H), 7.34-7.19 (m, 5H), 5.42-5.40 (m, 1H), 4.43-4.36 (m, 1H), 2.85-2.75 (m, 2H), 2.61-2.40 (m, 2H), 2.19-2.06 (m, 1H), 2.01-1.88 (m, 1H). EIMS *m/z* (relative intensity): 202 (M^+, 6.23), 158

(5.24), 130 (16.72), 117 (7.72), 104 (9.89), 91 (100.00), 77 (5.84), 69(6.88).

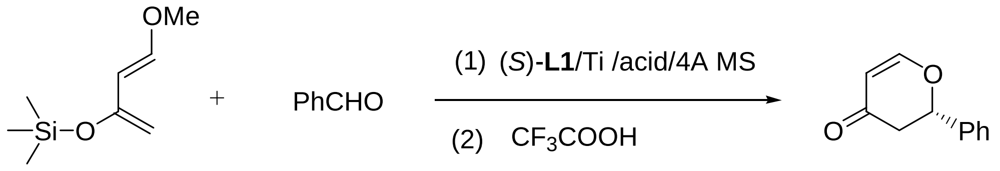
Enantiomeric excess was determined by HPLC on Chiralcel OD column, hexane : isopropanol = 90 : 10, flow rate = 1.0 mL/min, t_{R1} = 18.583 min (*S*), t_{R2} = 32.567 min (*R*).

The Effect of the Ligands on the Yield and Enantioselectivity of HDA Reaction between 1 and 2a



Ligand	Yield(%)	Ee(%)	Ligand	Yield(%)	ee(%)
L1	80	85	**L12**	59	42
L2	34	26	**L13**	70	85
L3	40	48	**L14**	39	3
L4	96	28	**L15**	49	60
L5	75	83	**L16**	39	6
L6	90	91	**L17**	39	7
L7	90	88	**L18**	75	4
L8	90	91	**L19**	78	30
L9	45	46	**L20**	100	59
L10	15	57	**L21**	69	65
L11	48	69	**L22**	28	16

The Effect of Carboxylic Acid Additives on the Yield and Enatioselectivity of the HDA Reaction between 1 and 2a



1 **2a** (*S*)-**3a**

Acid	Yield(%)	Ee(%)	Acid	Yield(%)	Ee(%)
A1	80	85	**A19**	100	48
A2	69	81	**A20**	46	46
A3	100	87	**A21**	100	97
A4	97	84	**A22**	100	88
A5	100	67	**A23**	100	83
A6	100	75	**A24**	24	5
A7	100	75	**A25**	16	8
A8	83	86	**A26**	57	50
A9	50	83	**A27**	39	40
A10	66	78	**A28**	58	1
A11	71	83	**A29**	71	22
A12	65	78	**A30**	51	37
A13	72	70	**A31**	48	47
A14	14	54	**A32**	62	50
A15	35	83	**A33**	23	39
A16	87	85	**A34**	9	39
A17	78	48	**A35**	13	53
A18	41	86	**A36**	17	46

The Search for Nonlinear Effect in the Catalytic System with L1/Ti/A21

Ee of (*S*)-**L1** (%)	Yield (%)	Ee (%) of **3a** (Configuration.)	Ee of (*R*)-**L1** (%)	Yield (%)	Ee(%) of **3a** (Configuration.)
0	69	55 (*S*)	0	69	55(*S*)
15	71	74(*S*)	25	39	36(*R*)
30	75	87(*S*)	50	48	42(*R*)
50	100	93(*S*)	75	78	60(*R*)
75	99.5	93(*S*)	100	87	76(*R*)
100	100	97(*S*)			

The Search for Nonlinear Effect in the Catalytic System with (*S*)-L1/Ti/A1

Ee of (*S*)-**L1** (%)	Yield (%)	Ee (%) of **3a** (Configuration.)	Ee of (*R*)-**L1** (%)	Yield (%)	Ee(%) of **3a** (Configuration.)
0	0	0	60	64	83.1(*S*)
15	39	39.1(*S*)	75	64.3	83.4(*S*)
30	53.6	53.3(*S*)	100	80	85(*S*)
45	62.7	82.7(*S*)			

References

[1] S. Danishefsky; T. Kitahara *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.

[2] E. J. Corey; C. L. Cywin; T. D. Roper *Tetrahedron Lett.*, **1992**, *33*, 6907-6910.

[3] T. Hanamoto; H. Furuno; Y. Sugimoto; J. Inanaga *SynLett.*, **1997**, 79-80.

[4] S. Danishefsky; N. Kato; D. Askin; J. F. Kerwin Jr. *J. Am. Chem. Soc.*, **1982**, *104*, 360-362.

[5] B. Wang; X. Feng; X. Cui; H. Liu; Y. Jiang *Chem. Commun.*, **2000**, 1605-1606.

[6] S. E. Schaus; J. Branalt; E. N. Jacobsen *J. Org. Chem.*, **1998**, *63*, 403-405.