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Quasi Solvent-free Enantioselective Carbonyl-Ene Reaction Using Extremely Low Catalyst Loading

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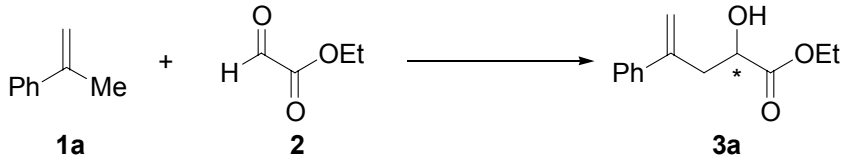
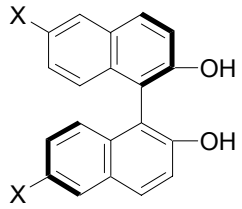
General methods. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM300 at 25°C. Chemical shifts were expressed in ppm with TMS as an internal standard (δ = 0 ppm) for ^{1}H NMR. Optical rotation was measured with a PE-341 automatic polarimeter. Liquid chromatographic analyses were conducted on a JASCO 1580 system. EI Mass spectra were obtained on a HP5989A spectrometer. IR spectra were taken on a Bio-Rad FTS-185 instrument. All the experiments which were 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 over sodium benzophenone ketyl.

Materials. (*R*)-BINOL (**L1**) were prepared by optical resolution with (*S*)-5-oxopyrrolidine-2-carboxanilide through molecular complexation.[1] Ligands **L2-L12** were prepared following the literature procedures.[2-6] Ethyl glyoxylate was obtained by the oxidation of diethyl tartrate with HIO_4 according to the literature method.[7]

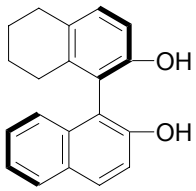
Creation of the chiral catalyst library and high throughput evaluation of the library



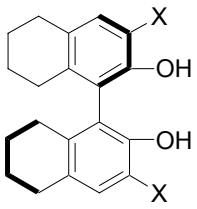
1a **2** **3a**



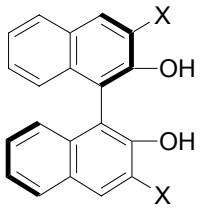
L1: X = H
L2: X = Br



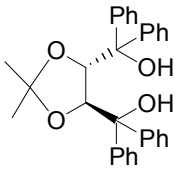
L3



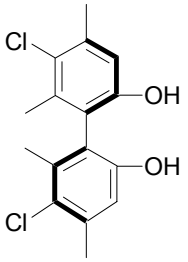
L4: X = H
L5: X = Br



L6: X = CH_3
L7: X = Br
L8: X = Ph



L9



L10

Ligands **L1**-**L10** were dissolved in dry toluene to make the solutions with the concentration of 0.05 M and these solutions were kept in glove box for use. The chiral catalyst library was created by combining one diol ligand (**L*m***) with $Ti(O^iPr)_4$ and an alternative diol ligand (**L*n***) in parallel style. To a 1.5-mL polypropylene microtube were added 0.05 M toluene solution of **L*m*** (50 μL, 0.0025 mmol), **L*n*** (50 μL, 0.0025 mmol) and 0.5-M solution of $Ti(O^iPr)_4$ in dichloromethane (5 μL, 0.0025 mmol) sequentially in the glove box. The mixture was kept at room temperature for 2 hrs and a red solution was formed, from which 50 μL of the catalyst solution (0.00125 mmol) was transferred to another1.5-mL polypropylene microtube. After the temperature of the catalyst solution was cooled to 0 °C, α-methylstyrene (165 μL, 1.25 mmol) and freshly distilled ethyl glyoxylate (200 μL, 2.5 mmol) were charged quickly. The reaction mixture was kept at 0 °C for 24 hrs and then diluted with hexane/isopropanol mixed solvent. The enantiomeric excess of the product was determined on a JASCO HPLC1500 with autosampler on a Chiralcel OJ column: eluent, hexane/2-propanol (97:3); flow rate, 0.7 mL/min; UV detection at λ = 254 nm; t_R ((*S*)-**3a**) =

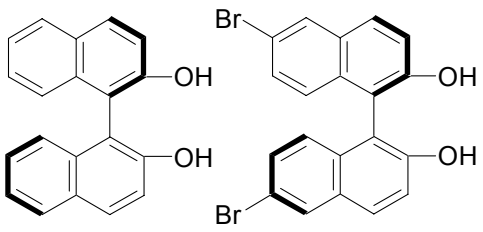
23.366 min (minor), t_R ((*R*)-**3a**) = 30.758 min (major). The results of primary screening of chiral catalyst library were summarized in Table 1.

Table 1. High throughput screening of chiral catalyst library (the *ee* of **3a** in the presence of 0.1 mol% of catalysts, "+" and "–" represent *R* and *S* configurations, respectively.)

ligand	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**L10**
L1	96.2	99.2	95.4	91.9	96.6	94.6	97.3	96.5	73.6	96.8
L2		95.8	99.0	97.8	89.2	95.8	95.6	96.4	76.5	97.4
L3			1.5	-36.5	3.3	81.5	66.2	84.7	-20	43.5
L4				91.0	2.4	34.8	2.9	21.3	--[a]	-85.5
L5					36.7	-17	-4.0	-15.7	-45.5	--[a]
L6						34.8	-16.7	-7.0	-1.5	39.4
L7							42.4	-13	11.5	2.0
L8								-43.2	4.3	-6.1
L9									36.7	-56.3
L10										--[a]

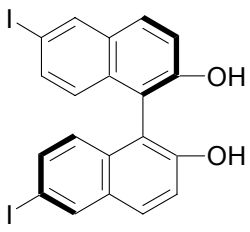
[a] No product was observed.

In the primary screening, as summarized in Table 1, the modification of diol ligand at 6,6'-positions of BINOL with Br is quite effective for the reaction. With the leading results mentioned above, we set up the secondary generation library of chiral ligands with various electron-withdrawing groups at 6,6'-position of BINOL. Following the similar procedure mentioned above, the catalysts generated with the ligands shown below were screened at 0.01 mol % level. Under this experimental condition, the solvent volume from the catalyst is about 1.3% of whole reaction system. The results were summarized in Table 2.

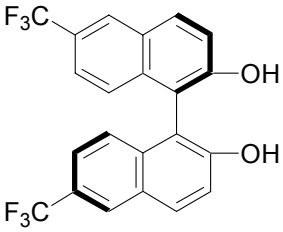


L1

L2



L11



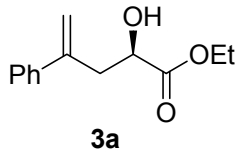
L12

Table 2. Quasi solvent-free enantioselective carbonyl-ene reaction (the *ee* of (*R*)-**3a** in the presence of 0.01 mol% of catalysts)

	L1	**L2**	**L11**	**L12**
L1	95.3	95.2	96.5	96.2
L2		96.4	96.1	96.1
L11			97.1	97.7
L12				94.9

Large-scale preparation of (*R*)-Ethyl 2-hydroxy-4-phenyl-4-pentenate (3a). To a solution of 6,6'-I_2-BINOL (27 mg, 0.05 mmol) and 6,6'-$(CF_3)_2$-BINOL (21 mg, 0.05 mmol) in toluene (1 mL) was added 0.5 M Ti(O*i*Pr)$_4$ in CH_2Cl_2 (100 μL, 0.05 mmol) and the mixture was stirred for 2 hrs at room temperature. The mixture was cooled to 0°C and then olefin **1a** (12.5 mL, 0.1 mol) and ethyl glyoxylate (15 mL, 0.2 mol) were added. After stirring for 48 hrs at 0°C, the reaction mixture was directly submitted to the silica gel flash column separation with EtOAc/hexane (1:4) as eluent to give 22 g of (*R*)-**3a** (>99% yield with 95% ee).

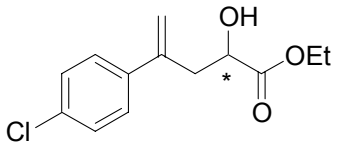
Characterization of the carbonyl-ene reaction products



3a

(*R*)-Ethyl 2-hydroxy-4-phenyl-4-pentenate (3a).[8] 95% ee. $[\alpha]^{25}_D$ = 1.84 (c 1.14, C_6H_6). IR (KBr) ν_{max} 3475, 3084, 3058, 2984, 2939, 1737, 1630, 1496, 1446, 1372, 1267, 1210, 1114, 1030, 905, 780 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.46-7.28 (m, 5H), 5.42 (d, *J* = 1.5 Hz, 1H), 5.23 (d, *J* = 0.6 Hz, 1H), 4.33-4.21 (m, 1H), 4.14-4.06 (m, 3H), 3.13 (dd, *J* = 4.5 Hz, 13.5 Hz, 1H), 2.88 (dd, *J* = 8.1 Hz, 13.5 Hz, 1H), 2.76 (s, 1H), 1.26 (t, *J* = 7.2 Hz, 3H). EIMS *m/z* (relative intensity): 220 (M^+, 38.62), 202 (25.82), 174 (11.50), 147 (45.90), 129 (100.00), 119 (63.65), 115 (41.90), 103 (42.58), 91 (88.83), 77 (45.74).

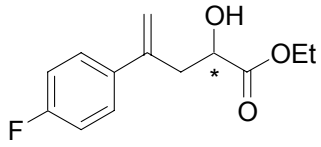
Enantiomeric excess was determined by HPLC on Chiralcel OJ column, hexane : isopropanol = 97 : 3, flow rate = 0.7 mL/min, t_{R1} = 23.366 min (minor), t_{R2} = 30.758 min (major).



3b

Ethyl 2-hydroxy-4-(4-chlorophenyl)-4-pentenate (3b).[9] 99.4% ee. $[\alpha]^{25}_{D}$ = -4.20 (c 2.30, C_6H_6). IR (KBr) ν_{max} 3477, 3088, 2984, 2937, 1902, 1734, 1629, 1493, 1446, 1396, 1299, 1266, 1210, 1114, 1093, 1013, 908, 837, 738 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.45-7.28 (m, 4H), 5.32 (dd, *J* = 4.9 Hz, 1.4 Hz, 2H), 4.28-4.25 (m, 1H), 4.20-4.05 (m, 2H), 3.05 (dd, *J* = 14.4 Hz, 5.7 Hz, 1H), 2.86-2.76 (m, 2H), 1.27 (t, *J* = 6.9 Hz, 3H). EIMS *m/z* (relative intensity): 254 (M^+, 67.21), 236 (17.96), 208 (13.54), 181 (90.14), 163 (100.00), 153 (71.62), 139 (38.51), 125 (62.98), 115 (64.12), 101 (35.84), 75 (42.44).

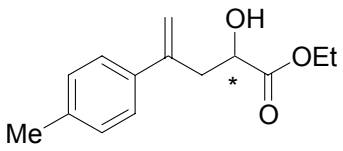
Enantiomeric excess was determined by HPLC on Chiralcel OJ column, hexane : isopropanol = 97 : 3, flow rate = 0.7 mL/min, t_{R1} = 19.700 min (minor), t_{R2} = 22.525 min (major).



3c

Ethyl 2-hydroxy-4-(4-fluorophenyl)-4-pentenate (3c).[9] 98.4% ee. $[\alpha]^{25}_{D}$ = 2.54 (c 1.18, C_6H_6). IR (KBr) ν_{max} 3467, 3087, 2984, 2939, 1894, 1737, 1630, 1737, 1630, 1603, 1510, 1301, 1268, 1225, 1162, 1112, 1033, 1015, 907, 842, 823 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H), 7.05-6.99 (m, 2H), 5.27(dd, *J* = 4.5 Hz, 1.2 Hz, 2H), 4.27-4.24 (m, 1H), 4.22-4.03 (m, 2H), 3.04 (dd, *J* = 14.7 Hz, 4.5 Hz, 1H), 2.85-2.73 (m, 2H), 1.26 (t, *J* = 4.2 Hz, 1H). EIMS *m/z* (relative intensity): 238 (M^+, 32.54), 220 (17.09), 192 (8.78), 175 (7.32), 165 (45.13), 147 (100.00), 136 (59.65), 121 (36.32), 109 (86.52), 96 (23.34), 75 (39.69).

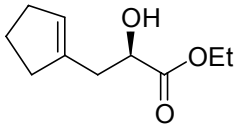
Enantiomeric excess was determined by HPLC on Chiralcel OJ column, hexane : isopropanol = 97 : 3, flow rate = 0.7 mL / min, t_{R1} = 20.683 min (minor), t_{R2} = 22.967 min (major).



3d

Ethyl 2-hydroxy-4-(4-tolyl)-4-pentenate (3d).[9] 97.1% ee. $[\alpha]^{25}_{D}$ = -6.10 (c 1.00, C_6H_6). IR (KBr) ν_{max} 3472, 3087, 3026, 2980, 2927, 2873, 1736, 1628, 1514, 1446, 1370, 1301, 1267, 1207, 1112, 1091, 1034, 952, 902, 826, 736 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.35 (d, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.30 (dd, *J* = 6.4 Hz, 1.5 Hz, 2H), 4.31-4.28 (m, 1H), 4.20-4.06 (m, 2H), 3.09 (dd, *J* = 14.4 Hz, 4.5 Hz, 1H), 2.89-2.75 (m, 2H), 2.38 (s, 3H), 1.29 (t, *J* = 6.9 Hz, 3H). EIMS *m/z* (relative intensity): 234 (M^+, 48.35), 216 (77.14), 187 (10.47), 161 (51.16), 143 (100.00), 132 (57.96), 128 (30.06), 115 (73.56), 105 (59.36), 91 (75.05), 77 (17.22).

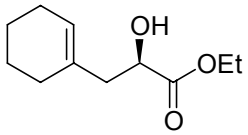
Enantiomeric excess was determined by HPLC on Chiralcel OJ column, hexane : isopropanol = 97 : 3, flow rate = 0.7 mL/min, t_{R1} = 23.133 min (minor), t_{R2} = 25.383 min (major).



3e

(*R*)-Ethyl 3-(1'-cyclopentenyl)-2-hydroxypropionate (3e).[8] 91.6% ee. $[\alpha]^{25}_{D}$ = 6.54 (c 0.78, C_6H_6). IR (KBr) ν_{max} 3487, 3403, 1734, 1611, 1516, 1364,1176, 1071, 962, 827 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (s, 1H), 4.34-4.21 (m, 3H), 2.85 (m, 1H), 2.60-2.52 (m, 2H), 2.36-2.26 (m, 2H), 1.93-1.83 (m, 2H), 1.31 (t, *J* = 6.9 Hz, 3H). EIMS *m/z* (relative intensity): 184 (M^+, 7.95), 166 (89.16), 137 (47.64), 120 (40.18), 111 (28.00), 104 (7.31), 93 (44.70), 81 (100.00), 67 (79.28).

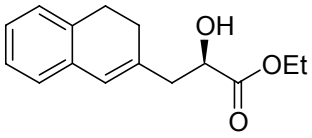
Enantiomeric excess was determined by chiral GC on Chiralsil-DEX CB column, initial T = 130 °C, hold 2 min, 1 °C/min to 160 °C, hold 10 min, t_{R1} = 16.735 min (major), t_{R2} = 17.628 min (minor).



3f

(*R*)-Ethyl 3-(1'-cyclohexenyl)-2-hydroxypropionate (3f).[8] 91.8% ee. $[\alpha]^{25}_{D}$ = 6.10 (c 1.11, C_6H_6). IR (KBr) ν_{max} 3456, 2983, 2935, 1829, 1748, 1447, 1373, 1216, 1098, 1029, 859 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 5.51 (s,1H), 4.33-4.19 (m, 3H), 3.01 (d, *J* = 5.4 Hz, 1H), 2.58-2.51 (m, 2H), 2.31-2.28 (m, 4H), 1.92-1.85 (m, 2H), 1.27 (t, *J* = 5.7 Hz, 3H). EIMS *m/z* (relative intensity): 198 (M^+, 8.85), 180 (100.00), 151 (39.40), 131 (14.62), 125 (18.86), 107 (29.78), 103 (74.00), 95 (99.46), 75 (90.90), 67 (39.13).

Enantiomeric excess was determined by chiral GC on Chiralsil-DEX CB column, initial T = 130 °C, hold 2 min, 1 °C/min to 160 °C, hold 10 min, t_{R1} = 24.617 min (major), t_{R2} = 25.770 min (minor).

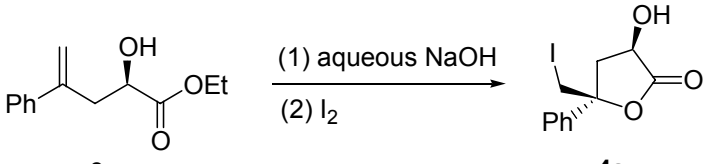


3g

(*R*)-Ethyl 3-(3,4-dihydronaphthalen-2-yl)-2-hydroxypronate (3g).[8] 96.3% ee. $[\alpha]^{25}_{D}$ = 13.7 (c 1.94, C_6H_6). IR (KBr) ν_{max} 3470, 3018, 2934, 2832, 1733, 1622, 1488, 1448, 1370, 1276, 1211, 1097, 941, 865, 817, 763, 738 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 7.30-7.27 (m, 1H), 7.24-7.18 (m, 1H), 7.17-7.14 (m, 2H), 6.00 (t, *J* = 4.5 Hz, 1H), 4.38-4.36 (m, 1H), 4.22-4.10 (m, 2H), 3.04 (dd, *J* = 14.4 Hz, 4.5 Hz, 1H), 2.79-2.71 (m, 4H), 2.31-2.25 (m, 2H), 1.27 (t, *J* = 7.5 Hz, 3H). EIMS *m/z* (relative intensity): 246 (M^+, 45.52), 228 (8.95), 199 (.7.12), 154 (18.62), 143 (100.00), 128 (93.25), 115 (25.04), 104 (34.26), 91 (11.44), 76 (24.43).

Enantiomeric excess was determined by HPLC on Chiralcel OJ column, hexane : isopropanol = 97 : 3, flow rate = 0.7 mL/min, t_{R1} = 18.925 min (minor), t_{R2} = 22.783 min (major).

Iodolactionization of 2-hydroxy-4-phenyl-pent-4-enoic acid ethyl ester (4a)



3a **4a**
95% yield
83:17 de

Aqueous solution of KOH (20 %) was added to a methanol (2 mL) solution of **3a** (100 μL, 0.47 mmol) and the mixture was heated to 40 °C. The stirring was continued for 3 hrs, and the solution was acidified with 1-M HCl to pH = 3. The resulting mixture was extracted with Et_2O (3 × 15 mL), and the organic phase was dried over anhydrous Na_2SO_4. After removal of solvent, the residue (91 mg, 100%) could be used without further purification.

The acid (81mg, 0.42 mmol) was dissolved in 4 mL of acetonitrile, to which the iodine (200 mg, 0.79 mmol) and sodium bicarbonate (200 mg, 2.38 mmol) were added. The mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ and the mixture was extracted with Et_2O. The orange extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel using 2:1 hexane/EtOAc as eluent to afford 3-hydroxy-5-iodomethyl-5-phenyl-4,5-dihydrofuran-2-one (**4a**) (127 mg, 95%): IR (KBr) ν_{max} 3491, 2933, 1774, 1495, 1448, 1413, 1251, 1185, 1145, 1119, 1019, 990, 917, 852, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.38 (m, 5H), 4.41 (dd, J = 10.8 Hz, 8.1 Hz, 1H), 3.66 (d, J = 4.5 Hz, 1H), 3.13 (dd, J = 12.6Hz, 8.1 Hz, 1H), 2.71 (dd, J = 12.9 Hz, 10.8 Hz, 1H). EIMS *m/z* (relative intensity): 318 (M^+, 1.44), 177 (30.78), 163 (70.31), 149, (17.39), 119 (57.02), 105 (87.87), 91 (100.00), 77 (46.03). HRMS (EI) calcd for $C_{11}H_{11}IO_3$ (M^+): 317.9753. Found: 317.9762.

X-Ray crystallographic data for 4a: $C_{11}H_{11}IO_3$, formula weight 318.10, forms monoclinic crystals, space group $P2_1$, with a = 13.7422(16) Å, b = 5.7299(7) Å, c = 14.1629(17) Å, V = 1115.2(2) $Å^3$; ρ_{calc} = 1.895 g cm^{-3}, Z = 4. A total of 6736 reflections were measured on a Bruker Smart CCD area detector at 293(2)K using Mo-Kα radiation (λ = 0.71073 Å) with $2\theta_{max}$ = 56.6°, giving 4787 independent reflections of which 4099 have I > 2.00σI, R_{int} = 0.1110. The structure was solved by direct methods (SHELXS-97) and refined by full matrix least squares to R = 0.0549, R_w = 0.1209. Goodness of fit on F^2 is 1.001.

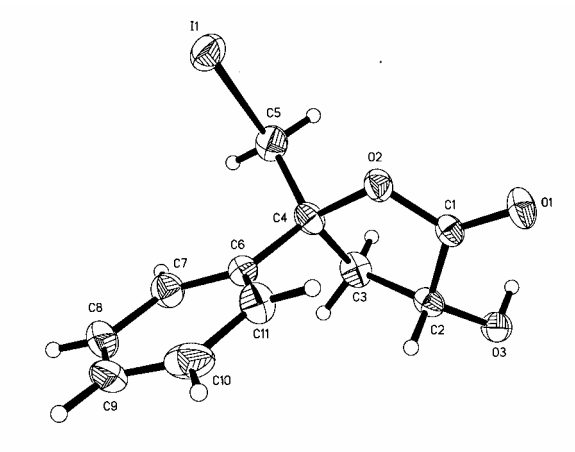


Figure 3. X-Ray crystal Structure of 3-Hydroxy-5-iodomethyl-5-phenyl-dihydro-furan-2-one (4a)

References

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