Supporting Information

Dramatic Ligand Effect in Catalytic Asymmetric Reductive Aldol Reaction of Allenic Esters to Ketones

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General: ^1H NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^1H NMR, 125.65 MHz for ^{13}C NMR and 202.35 MHz for ^{31}P NMR. Chemical shifts were reported downfield from TMS ($\delta = 0$ ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ^{31}P NMR were carried out with phosphoric acid ($\delta = 0$ ppm) as an external standard. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC analysis was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254nm or 220nm; mobile phase, hexane–2-propanol. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Normal glassware can be used to conduct the reaction in this manuscript. $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}$ was synthesized following the reported procedure.¹ CuOAc was purchased from Wako Pure Chemical Industries, Ltd. (*R*)-DTBM-SEGPHOS was provided from

Takasago International Corporation. Taniaphos ligands were synthesized following literature method² except for commercially available Taniaphos **L1** from Strem Chemicals, Inc. Other chiral and achiral phosphine ligands were also purchased from Strem. Ethyl 2,3-butadienoate was purchased from Aldrich Chemical Company and other allenic esters were synthesized following the reported literature.³ Pinacolborane was purchased from Aldrich and used as received. Dimethylzinc and diethylzinc (1.0 M in hexane solution) were purchased from Kanto Chemical Co., Inc. and used as received.

1-1. General procedure for the optimization of reaction conditions

A typical procedure for reductive aldol reaction of ethyl 2,3-butadienoate to acetophenone: A catalyst solution was generated from a copper precursor (0.005 mmol, 2.5 mol%), a chiral ligand (0.01 mmol, 5.0 mol%) and additives in a degassed solvent under stirring at room temperature for 10 min. Ethyl 2,3-butadienoate (0.3 mmol, 1.5 equiv.) and acetophenone (0.2 mmol) were then added successively to the catalyst solution. Another 10 min later, reductive reagent pinacolborane (0.32 mmol, 1.6 equiv.) was added slowly to the reaction mixture via syringe pump for 4 h at the reaction temperature. The mixture was allowed to stir at this temperature for further 12 h. After confirming that the ketone completely disappeared by TLC analysis, H₂O was added. The product was extracted with dichloromethane and the combined organic layer was washed with brine. The organic layer was dried over Na₂SO₄. After filtration and evaporation, nmr yield, regio- and diastereoselectivities were determined by nmr analysis of the crude product with TMSOTMS as an internal standard. And purification by silica gel column chromatography (eluent: AcOEt/hexane = 1/10 to 1/5) gave γ -cis adduct **3a**, γ -trans adduct **4a** and α adducts **5a**, **6** (diastereomeric mixture). Among those aldol adducts, α adducts **5a** and **6** were slightly sensitive to silica gel. To avoid the epimerization and to determine the enantiomeric excess of **5a**, hydrogenation conversion from crude α adducts **5a** and **6** to **11a** (*syn* and *anti*) was performed immediately after reductive aldol reaction. The hydrogenation reaction conditions are: 10 mol % Pd/C as a catalyst, in the presence of atmospheric H₂ in THF at room temperature. Spectroscopic data of those compounds are as follows.

(5*R*)-(Z)-ethyl 5-hydroxy-5-phenylhex-2-enoate (**3a**)

¹H NMR (500 MHz, CDCl₃) δ : 1.22 (t, *J* = 7.3 Hz, 3H), 1.53 (s, 3H), 2.97-3.01 (m, 2H), 3.16 (dd, *J*₁ = 14.6 Hz, *J*₂ = 8.4 Hz, 1H), 4.11 (q, *J* = 7.3 Hz, 2H), 5.83 (d, *J* = 10.5 Hz, 1H), 6.07-6.13 (m, 1H), 7.15-7.28 (m, 3H), 7.41 (d, *J* = 9.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 14.10, 30.48, 42.81, 60.18, 74.47, 122.44, 124.64, 126.57, 128.09, 144.96, 147.28, 167.00; IR (neat, cm⁻¹): ν 701, 1193, 1716, 2979, 3474; MS (ESI) *m/z* 258.9 (M+Na)⁺; HRMS (FAB) calcd for C₁₄H₁₇O₂ (M-OH)⁺ 217.1223. Found 217.1252; [α]_D²³ = +67.0 (*c* = 1.31, CHCl₃) for 99% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, *n*-hexane / *i*-PrOH = 49 / 1, *t* = 37.5 min (major), 44.0 min (minor). λ = 220nm.

(*E*)-ethyl 5-hydroxy-5-phenylhex-2-enoate (**4a**)

¹H NMR (500 MHz, CDCl₃) δ : 1.18 (t, *J* = 7.4 Hz, 3H), 1.51 (s, 3H), 1.99 (s, 1H), 2.56-2.61 (m, 1H), 2.64-2.68 (m, 1H), 4.06 (q, *J* = 7.4 Hz, 2H), 5.77 (d,

$J = 15.5$ Hz, 1H), 6.73-6.80 (m, 1H), 7.14-7.38 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 14.19, 29.80, 46.81, 60.25, 74.04, 124.59, 124.84, 127.02, 128.36, 143.90, 146.97, 166.11; IR (KBr, cm^{-1}): ν 701, 765, 1178, 1268, 1718, 2342, 2978, 3475; MS (ESI) m/z 256.8 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 217.1223. Found 217.1220; $[\alpha]_{\text{D}}^{23} = -3.5$ ($c = 1.15$, CHCl_3) for 17% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.8 mL / min, n -hexane / i -PrOH = 20 / 1, $t = 13.7$ min (minor), 15.4 min (major). $\lambda = 220$ nm.

Ethyl 2-(1-hydroxy-1-phenylethyl)but-3-enoate (5a + 6a) (underlined chemical shifts for major isomer **5a** of diastereomeric mixture)

^1H NMR (500 MHz, CDCl_3) δ : 0.85 (t, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.0$ Hz, 3H), 1.35 (s, 3H), 1.53 (s, 3H), 3.35 (d, $J = 8.2$ Hz, 1H), 3.47 (d, $J = 9.2$ Hz, 1H), 3.76-3.90 (m, 2H), 4.00 (s, 1H), 4.08-4.16 (m, 2H), 4.26 (s, 1H), 4.89 (d, $J = 17.0$ Hz, 1H), 4.97 (d, $J = 10.4$ Hz, 1H), 5.27 (t, $J = 10.4$ Hz, 2H), 5.65-5.72 (m, 1H), 6.01-6.08 (m, 1H), 7.13-7.37 (m, 5H+5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 13.87, 14.25, 28.00, 29.34, 59.85, 60.45, 60.96, 61.31, 74.95, 75.24, 119.65, 120.85, 124.86, 125.23, 126.93, 127.01, 128.14, 128.27, 132.22, 132.26, 144.82, 147.09, 174.02, 174.14; IR (neat, cm^{-1}): ν 700, 1026, 1183, 1324, 1371, 1711, 2935, 2981, 3498; MS (ESI) m/z 256.9 ($\text{M}+\text{Na}$) $^+$.

Ethyl 2-ethyl-3-hydroxy-3-phenylbutanoate (11a-syn + 11a-anti) (underlined chemical shifts for major isomer **7a-syn** of diastereomeric mixture)

^1H NMR (500 MHz, CDCl_3) δ : 0.73 (t, $J = 7.5$ Hz, 3H), 0.87 (t, $J = 7.0$ Hz, 3H), 0.92 (t, $J = 7.6$ Hz, 3H), 1.12-1.18 (m, 1H), 1.30 (t, $J = 7.3$ Hz, 3H), 1.50 (s, 3H), 1.51 (s, 3H), 1.63-1.69 (m, 1H), 1.79-1.91 (m, 1H), 2.64 (dd, $J_1 = 11.6$ Hz, $J_2 = 3.7$ Hz, 1H), 2.77 (dd, $J_1 = 11.0$ Hz, $J_2 = 4.2$ Hz, 1H), 3.71 (s, 1H), 3.79-3.89 (m, 2H), 3.88 (s, 1H), 4.24 (q, $J = 7.5$ Hz, 2H), 7.13-7.37 (m, 5H+5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.01, 12.23, 13.73, 14.23, 20.40, 20.78, 27.04, 30.13, 56.80, 57.50, 60.17, 60.64, 74.37, 74.82, 124.65, 124.72, 126.51, 126.60, 127.87, 127.99, 141.90, 145.34, 176.07, 176.61; IR (neat, cm^{-1}): ν 701, 1188, 1374, 1706, 2970, 3503; MS (ESI) m/z 258.9 ($\text{M}+\text{Na}$) $^+$; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 25.5$ min (*syn* major), 27.6 min (*syn* minor), 32.5 min, 34.7 min. $\lambda = 220$ nm.

1-2. Ligand effect on regioselectivity in this reductive aldol reaction

entry	P* ligand	nmr yield (%)		
		3a	4a	5a / 6
1	(R)-DTBM-SEGPHOS	46 (99% ee)	<4	20 (3% ee)/2 (7% ee)
2	(R)-SEGPHOS	59	15	18/8
3	(R)-Tol-BINAP	24 (98% ee)	20 (26% ee)	30 (30% ee)/8 (7% ee)
4	(S,S)-iPr-Duphos	23 (87% ee)	8 (33% ee)	55/16
5	(R,R)-Et-Duphos	-	-	36 (8% ee)/13 (10% ee)
6	(R,R)-Me-Duphos	-	-	59 (6% ee)/25 (8% ee)
7	(S,S)-DIOP	-	92 (2% ee)	5/3
8	Taniaphos L1	-	-	86 (40% ee) /14 (7% ee)
9	(R)-MOP	-	7	60/37

^a slow additon for 4 h, then stirred for further 12 h.

2-1. Copper salt and additive effects in γ -cis selective reductive aldol reaction

entry	Cu salt	P additive	nmr yield (%)		
			3a	4a	5a / 6
1	CuF(PPh ₃) ₃ •2EtOH	-	46 (99% ee)	<4	20/2
2	CuF(PPh ₃) ₃	-	33	<4	9/3
3 ^b	CuF ₂ •2H ₂ O	-	trace	trace	22/9
4	CuOAc	-	32	<3	14/4
5 ^c	CuOTf/ KO ^t Bu	-		No TM	
6	CuOAc	PPh ₃	60 (99% ee)	-	6/-
7	CuOAc	PCy₃	90 (99% ee)	-	9/-
8	CuOAc	P(O)Ph ₃	23	12	42/24
9	CuOAc	P ^t Bu ₃	4	-	60/36
10	CuOAc	PEt ₃	30	-	10/2
11	CuOAc		34	-	4/-
12	CuOAc		76	-	5/-

^a Slow additon for 4 h, then stirred for further 12 h. ^b Catalyst was prepared in refluxing methanol for 2 h followed by azeotropic evaporation with toluene. ^c (R)-Tol-BINAP was used instead.

2-2. Generality of ketones in γ -cis selective reductive aldol reaction

General procedure for γ -cis selective reductive aldol reaction to ketones: A catalyst solution was generated from CuOAc (0.02 mmol, 2.5 mol%), (*R*)-DTBM-SEPHOS (0.04 mmol, 5.0 mol%) and PCy₃ (0.04 mmol, 5.0 mol%) in degassed THF (1.0 mL) under stirring at room temperature for 10 min. Ethyl 2,3-butadienoate (1.2 mmol, 1.5 equiv.) and a ketone (0.8 mmol) were then added successively to the catalyst solution. Another 10 min later, pinacolborane (1.28 mmol, 1.6 equiv.) was added slowly to the reaction mixture via syringe pump for 4 h at the reaction temperature. The mixture was allowed to stir at this temperature for further 12 h. After confirming that the ketone completely disappeared by TLC analysis, H₂O was added. The product was extracted with dichloromethane and the combined organic layer was washed with brine. The organic layer was dried over Na₂SO₄. After filtration and evaporation, the nmr yield and regioselectivity were determined by nmr analysis of the crude product with TMSOTMS as an internal standard. Purification by silica gel column chromatography (eluent: AcOEt/hexane = 1/10 to 1/5) gave the pure γ -cis reductive aldol product for spectroscopic data and enantiomeric excess determination as well.

(*Z*)-ethyl 5-(4-chlorophenyl)-5-hydroxyhex-2-enoate (3b)

¹H NMR (500 MHz, CDCl₃) δ : 1.27 (t, *J* = 7.2 Hz, 3H), 1.56 (s, 3H), 3.00 (dd, *J*₁ = 14.0 Hz, *J*₂ = 8.0 Hz, 1H), 3.17 (dd, *J*₁ = 14.0 Hz, *J*₂ = 8.0 Hz, 1H), 3.25 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 5.89 (d, *J* = 11.6 Hz, 1H), 6.08-6.14 (m, 1H), 7.28 (d, *J* = 9.1 Hz, 2H), 7.40 (d, *J* = 9.1 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 14.06, 30.52, 42.69, 60.30, 74.23, 122.75, 126.23, 128.15, 132.33, 144.40, 145.67, 166.98; IR (neat, cm⁻¹): ν 821, 1094, 1196, 1715, 2979, 3460; MS (ESI) *m/z* 290.92 (M+Na)⁺; HRMS (FAB) calcd for C₁₄H₁₆ClO₂ (M-OH)⁺ 251.0833. Found 251.0836; [α]_D²³ = +83.8 (*c* = 0.95, CHCl₃) for 98% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, *n*-hexane / *i*-PrOH = 49 / 1, *t* = 42.7 min (major), 48.0 min (minor). λ = 220nm.

(*Z*)-ethyl 5-hydroxy-5-*p*-tolylhex-2-enoate (3c)

¹H NMR (500 MHz, CDCl₃) δ : 1.37 (t, *J* = 7.3 Hz, 3H), 1.67 (s, 3H), 2.42 (s, 3H), 3.01 (s, 1H), 3.13 (dd, *J*₁ = 15.0 Hz, *J*₂ = 7.0 Hz, 1H), 3.30 (dd, *J*₁ = 15.0 Hz, *J*₂ = 7.0 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 5.97 (d, *J* = 11.5 Hz, 1H), 6.22-6.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 14.10, 20.64, 30.55, 42.82, 59.98, 74.12, 122.31, 124.57, 128.78, 136.09, 144.26, 144.89, 166.99; IR (neat, cm⁻¹): ν 816, 1187, 1714, 2926, 2978, 3478; MS (ESI) *m/z* 270.98 (M+Na)⁺; HRMS (EI) calcd for C₁₅H₂₀O₃ (M)⁺ 248.1407. Found 248.1430; [α]_D²³ = +71.9 (*c* = 0.77, CHCl₃) for 97% ee; HPLC condition: Chiralcel OJ-H column, flow rate: 0.5 mL / min, *n*-hexane / *i*-PrOH = 49 / 1, *t* = 72.3 min (major), 94.3 min (minor). λ = 220nm.

(*Z*)-ethyl 5-(3-chlorophenyl)-5-hydroxyhex-2-enoate (3d)

¹H NMR (500 MHz, CDCl₃) δ : 1.22 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 2.94 (dd, *J*₁ = 14.4 Hz, *J*₂ = 7.6 Hz, 1H), 3.12 (dd, *J*₁ = 14.4 Hz, *J*₂ =

8.6 Hz, 1H), 3.25 (s, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 5.84 (d, $J = 11.3$ Hz, 1H), 6.03-6.09 (m, 1H), 7.12-7.34 (m, 3H), 7.42 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 14.16, 30.56, 42.70, 60.47, 74.38, 122.99, 123.01, 125.23, 126.80, 129.47, 134.23, 144.39, 149.68, 167.35; IR (neat, cm^{-1}): ν 699, 786, 1037, 1199, 1417, 1698, 2978, 3445; MS (ESI) m/z 291.0, 292.9 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{16}\text{ClO}_2$ ($\text{M}-\text{OH}$) $^+$ 251.0833. Found 251.0862; $[\alpha]_{\text{D}}^{28} = +73.4$ ($c = 1.22$, CHCl_3) for 99% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 49 / 1, $t = 34.5$ min (major), 40.8 min (minor). $\lambda = 220\text{nm}$.

(2Z, 6E)-ethyl 5-hydroxy-5-methyl-7-phenylhepta-2,6-dienoate (3e)

^1H NMR (500 MHz, CDCl_3) δ : 1.21 (t, $J = 7.0$ Hz, 3H), 1.36 (s, 3H), 2.55 (s, 1H), 2.85 (dd, $J_1 = 14.3$ Hz, $J_2 = 7.5$ Hz, 1H), 2.96 (dd, $J_1 = 14.3$ Hz, $J_2 = 8.0$ Hz, 1H), 4.10 (q, $J = 7.0$ Hz, 2H), 5.88 (d, $J = 11.5$ Hz, 1H), 6.22 (d, $J = 16.0$ Hz, 1H), 6.27-6.32 (m, 1H), 6.57 (d, $J = 16.0$ Hz, 1H), 7.13-7.32 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 14.13, 28.58, 41.35, 60.13, 73.16, 122.42, 126.39, 127.34, 127.53, 128.46, 135.92, 136.80, 144.77, 166.92; IR (neat, cm^{-1}): ν 694, 750, 1189, 1714, 2978, 3471; MS (ESI) m/z 282.97 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{19}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 243.1380. Found 243.1378; $[\alpha]_{\text{D}}^{23} = +62.1$ ($c = 1.24$, CHCl_3) for 84% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.7 mL / min, n -hexane / i -PrOH = 49 / 1, $t = 55.8$ min (major), 65.1 min (minor). $\lambda = 220\text{nm}$.

(Z)-ethyl 5-hydroxy-5-methyl-7-phenylhept-2-enoate (3f)

^1H NMR (500 MHz, CDCl_3) δ : 1.18-1.24 (m, 6H), 1.74-1.78 (m, 2H), 2.26 (s, 1H), 2.63-2.68 (m, 2H), 2.74 (dd, $J_1 = 14.5$ Hz, $J_2 = 8.0$ Hz, 1H), 2.87 (dd, $J_1 = 14.5$ Hz, $J_2 = 8.0$ Hz, 1H), 4.11 (q, $J = 7.0$ Hz, 2H), 5.91 (d, $J = 11.5$ Hz, 1H), 6.33-6.39 (m, 1H), 7.09-7.22 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 14.11, 26.80, 30.28, 40.60, 44.54, 60.05, 72.81, 122.35, 125.68, 128.26, 128.32, 142.29, 145.18, 166.93; IR (neat, cm^{-1}): ν 700, 1186, 1717, 2925, 3446; MS (ESI) m/z 284.99 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 245.1536. Found 245.1550; $[\alpha]_{\text{D}}^{23} = +2.4$ ($c = 0.41$, CHCl_3) for 96% ee; HPLC condition: Chiralcel OD-H column, flow rate: 0.7 mL / min, n -hexane / i -PrOH = 49 / 1, $t = 58.7$ min (major), 90.4 min (minor). $\lambda = 220\text{nm}$.

(Z)-ethyl 5-hydroxy-5-methylnona-2,8-dienoate (3g)

^1H NMR (500 MHz, CDCl_3) δ : 1.21 (s, 3H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.57-1.62 (m, 2H), 2.12-2.16 (m, 2H), 2.24 (s, 1H), 2.75 (dd, $J_1 = 14.5$ Hz, $J_2 = 8.0$ Hz, 1H), 2.85 (dd, $J_1 = 14.5$ Hz, $J_2 = 8.0$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 2H), 4.93 (dq, $J_1 = 10.0$ Hz, $J_2 = 1.2$ Hz, 1H), 5.02 (dq, $J_1 = 17.0$ Hz, $J_2 = 1.5$ Hz, 1H), 5.78-5.86 (m, 1H), 5.93 (d, $J = 11.5$ Hz, 1H), 6.36-6.42 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 14.14, 26.74, 28.27, 40.53, 41.62, 60.06, 72.85, 122.21, 138.70, 145.27, 166.86; IR (neat, cm^{-1}): ν 1187, 1717, 2929, 2977, 3474; MS (ESI) m/z 234.92 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3$ (M) $^+$ 212.1407. Found 212.1437; $[\alpha]_{\text{D}}^{23} = -1.5$ ($c = 0.55$, CHCl_3) for 89% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 118.3$ min (major), 130.9 min (minor). $\lambda = 220\text{nm}$.

(Z)-ethyl 5-hydroxy-5-methylnon-2-enoate (3h)

¹H NMR (500 MHz, CDCl₃) δ: 0.84 (t, *J* = 7.0 Hz, 3H), 1.14 (s, 3H), 1.18-1.34 (m, 7H), 1.42-1.45 (m, 2H), 2.10 (s, 1H), 2.69 (dd, *J*₁ = 15.0 Hz, *J*₂ = 7.5 Hz, 1H), 2.77 (dd, *J*₁ = 15.0 Hz, *J*₂ = 7.5 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 5.80 (d, *J* = 11.5 Hz, 1H), 6.32-6.37 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ: 13.95, 14.14, 23.13, 26.05, 26.79, 40.42, 42.41, 59.89, 72.96, 122.01, 145.52, 166.85; IR (neat, cm⁻¹): ν 1035, 1186, 1719, 2932, 2959, 3446; MS (ESI) *m/z* 236.95 (M+Na)⁺; HRMS (ESI) calcd for C₁₂H₂₁O₂ (M-OH)⁺ 197.1536. Found 197.1530; [α]_D²³ = -4.1 (*c* = 0.84, CHCl₃) for 88% ee; HPLC condition: Chiralpak AD-H column, flow rate: 0.5 mL / min, *n*-hexane / *i*-PrOH = 199 / 1, *t* = 107.3 min (major), 119.6 min (minor). λ = 220nm.

(Z)-ethyl 5-hydroxy-5,6-dimethylhept-2-enoate (3i)

¹H NMR (500 MHz, CDCl₃) δ: 0.86 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 1.06 (s, 3H), 1.17-1.24 (m, 5H), 1.69-1.73 (m, 1H), 2.73 (dd, *J*₁ = 13.0 Hz, *J*₂ = 8.0 Hz, 1H), 2.84 (dd, *J*₁ = 13.0 Hz, *J*₂ = 8.0 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 5.94 (d, *J* = 11.5 Hz, 1H), 6.40-6.46 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ: 14.16, 17.02, 17.53, 22.86, 37.98, 38.11, 60.07, 75.23, 122.01, 146.15, 167.09; IR (neat, cm⁻¹): ν 1032, 1733, 2923; MS (ESI) *m/z* 222.94 (M+Na)⁺; HRMS (EI) calcd for C₁₁H₂₀O₃ (M)⁺ 200.1407. Found 200.1421; [α]_D²⁵ = +15.6 (*c* = 1.0, CHCl₃) for 97% ee; HPLC condition: Chiralcel OD-H column, flow rate: 0.7 mL / min, *n*-hexane / *i*-PrOH = 99 / 1, *t* = 26.0 min (major), 32.6 min (minor). λ = 220 nm.

3-1. Synthesis of new Taniaphos ligands for α-selective reductive aldol reaction

General procedure for synthesis of Taniaphos type ligands:² Spectroscopic data of newly reported Taniaphos ligand **L3** are as follows.

(R)-(α-hydroxy-α-bromophenylmethyl)ferrocene (S1)

Known compound. Prepared following the procedure reported by Knochel et al.² Recrystallization from Hexane/Ether at -78°C afforded optically pure compound (recrystallization yield was over 80%).

(R)-(α-(1-morpholinyl)-α-bromophenylmethyl)ferrocene (S2)

Prepared following the procedure reported by Knochel et al.² To the mixture of pyridine (1.26 mL), alcohol **S1** (0.9 g, 2.43 mmol, 1.0 equiv.) and DMAP (cat.), acetic anhydride (0.54 mL, 5.71 mmol, 2.5 equiv.) was added at room temperature and stirred for 30 min. Volatiles were evaporated, then residue was dissolved in acetonitrile (30 mL)-water (5 mL) mixed solvent. To the solution,

morpholine (1.1 mL, 12.1 mmol, 5.0 equiv.) was added and stirred at room temperature overnight. The reaction mixture was then concentrated and extracted with diethyl ether. After washing with water and brine, the organic layer was dried over Na₂SO₄. Extract was filtered off, evaporated, and crude product was purified by short pad silical gel chromatography (eluent: AcOEt/hexane = 1/10 to 1/5) to give the amine **S2** as orange crystals in 88% yield (938 mg). ¹H NMR (500 MHz, CDCl₃) δ : 2.28-2.39 (m, 4H), 3.64 (t, *J* = 4.6 Hz, 4H), 3.85 (s, 5H), 4.20 (br, 1H), 4.25 (br, 2H), 4.30 (br, 1H), 4.63 (s, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ : 52.25, 66.33, 66.38, 67.12, 67.99, 68.59, 68.74, 71.07, 88.70, 125.33, 127.37, 128.41, 129.78, 132.55, 142.48; IR (neat, cm⁻¹): ν 476, 750, 1117, 2359, 2804, 2851, 2956; MS (ESI) *m/z* 352.8 (M-morpholine)⁺, 438.9 (M)⁺; HRMS (FAB) calcd for C₂₁H₂₂BrNOFe (M+H)⁺ 439.0229. Found 439.0218; [α]_D²³ = -46.5 (*c* = 1.26, CHCl₃).

1-(S_{FC})-bis(3,5-xylyl)phosphanyl-2-[(*R*)-(α -(1-morpholinyl)-*o*-bis(3,5-xylyl)phosphanylphenylmethyl)ferrocene (Taniaphos **L3**)

Prepared following the procedure reported by Knochel et al.² The amine **S2** (2.20 g, 5 mmol, 1.0 equiv.) was dissolved in anhydrous diethyl ether (20 mL) under argon and cooled to -78°C. Then *t*-BuLi (1.59 N in pentane, 11.0 mL, 17.5 mmol, 3.5 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred for 1 h. ClPAR₂ (Ar = 3,5-xylyl) (3.46 g, 12.5 mmol, 2.5 equiv.) was then added dropwise at -78°C, and the mixture was stirred at room temperature overnight. After hydrolysis, product was extracted with diethyl ether. The organic layer was washed with brine and dried over Na₂SO₄. Extract was filtered off, evaporated, and the crude mixture was purified by silica gel column chromatography twice (eluent: AcOEt/hexane = 1/20 to 1/10) to give bisphosphine **L3** as foamy orange solid in 30% yield (1.21 g). ¹H NMR (500 MHz, CDCl₃) δ : 2.09 (s, 6H), 2.22-2.27 (m, 14H), 2.30 (s, 6H), 2.42-2.48 (m, 2H), 2.98-3.04 (m, 2H), 3.21-3.27 (m, 2H), 3.72 (s, 5H), 3.96 (s, 1H), 4.30-4.32 (m, 1H), 4.52 (br, 1H), 5.86 (d, *J* = 9.2 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.70 (s, 1H), 6.84-7.11 (m, 10H), 7.19 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 21.16, 21.33, 21.37, 51.69, 66.87, 68.18, 70.00, 71.81, 126.51, 127.75, 129.14, 130.00-130.50 (m), 131.53-131.69 (m), 132.87, 133.05, 134.64, 136.50 (d, *J* = 7.3 Hz), 136.95 (d, *J* = 8.3 Hz), 137.42, 137.48, 138.33, 138.43, 138.65, 138.75, 138.88, 138.98; ³¹P NMR (202 MHz, CDCl₃) δ : -21.69 (d, *J* = 8.1 Hz), -15.16 (d, *J* = 10.1 Hz); IR (neat, cm⁻¹): ν 694, 732, 847, 909, 1115, 1451, 1581, 1597, 2855, 2915, 2951; MS (ESI) *m/z* 755.2 (M-morpholine)⁺, 841.3 (M)⁺; HRMS (FAB) calcd for C₅₃H₅₈NOP₂Fe (M+H)⁺ 842.3338. Found 842.3351; [α]_D²³ = +212.7 (*c* = 1.01, CHCl₃).

3-2. Generality of ketones in α -selective reductive aldol reaction

General procedure for α -selective reductive aldol reaction to ketones: A catalyst solution was generated from CuF•3PPh₃•2EtOH (0.02 mmol, 2.5 mol%) and Taniaphos ligand (0.04 mmol, 5.0 mol%) in degassed THF (0.5 mL) under stirring at room temperature for 10 min. Methyl 2,3-butadienoate (1.2 mmol, 1.5 equiv.) and a ketone (0.8 mmol) were then added successively to the catalyst solution. Another 10 min later, pinacolborane (1.28 mmol, 1.6 equiv.) was added slowly to the reaction mixture via syringe pump for 4 h at the reaction temperature. The mixture was allowed to stir at this temperature for further 12 h. After confirming that the ketone completely disappeared by TLC analysis, H₂O was added. The product was extracted with

dichloromethane and the combined organic layer was washed with brine. The organic layer was dried over Na₂SO₄. After filtration and evaporation, nmr yield, regio- and diastereoselectivities were determined by nmr analysis of the crude product with TMSOTMS as an internal standard. Purification by silica gel column chromatography (eluent: AcOEt/hexane = 1/10 to 1/5) gave pure α adducts **7** and **6** as diastereomeric mixture for spectroscopic data. Both stereochemistry⁴ and enantiomeric excess determination were performed after conversion to **12** (*syn* and *anti*) through hydrogenation with Pd/C. Both diastereomers of **7** (*syn* and *anti*) could be separated by silica gel column chromatography.

Methyl 2-(1-hydroxy-1-phenylethyl)but-3-enoate (7a + 6a') (underlined chemical shifts for major isomer of diastereomeric mixture)

(-)-(2R,3R)-Methyl 2-ethyl-3-hydroxy-3-phenylbutanoate (12a-syn) (major isomer)

(+)-Methyl 2-ethyl-3-hydroxy-3-phenylbutanoate (12a-anti) (minor isomer)

(+)-Methyl 2-(1-(4-chlorophenyl)-1-hydroxyethyl)but-3-enoate (7b) (major isomer)

Hz, 1H), 5.61-5.69 (m, 1H), 7.10-7.30 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ : 29.13, 52.19, 60.10, 74.53, 120.02, 126.61, 128.11, 131.58, 132.63, 143.15, 174.08; IR (neat, cm^{-1}): ν 833, 926, 1012, 1093, 1172, 1199, 1330, 1491, 1716, 2924, 2953, 3505; MS (ESI) m/z 276.9 (M^+Na); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{15}\text{ClO}_3$ (M) $^+$ 254.0705. Found 254.0709; $[\alpha]_{\text{D}}^{25} = +46.7$ ($c = 1.17$, CHCl_3) for 83% ee.

(-)-Methyl 3-(4-chlorophenyl)-2-ethyl-3-hydroxybutanoate (12b-syn) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 0.72 (t, $J = 7.6$ Hz, 3H), 1.08-1.19 (m, 1H), 1.46 (s, 3H), 1.62-1.66 (m, 1H), 2.61 (dd, $J_1 = 11.6$ Hz, $J_2 = 3.7$ Hz, 1H), 3.74 (s, 1H), 3.76 (s, 3H), 7.24-7.35 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.10, 20.86, 30.17, 51.74, 57.42, 74.21, 124.79, 126.37, 128.23, 132.50, 143.89, 177.02; IR (KBr, cm^{-1}): ν 579, 829, 1176, 1201, 1370, 1708, 2879, 2968, 3515; MS (ESI) m/z 279.1 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{17}\text{ClO}_3$ (M) $^+$ 256.0861. Found 256.0852; $[\alpha]_{\text{D}}^{27} = -21.8$ ($c = 1.24$, CHCl_3) for 83% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 14.2$ min (major), 16.4 min (minor). $\lambda = 220\text{nm}$.

(+)-Methyl 2-(1-(3-chlorophenyl)-1-hydroxyethyl)but-3-enoate (7d) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 1.56 (s, 3H), 3.38 (d, $J = 8.5$ Hz, 1H), 3.73 (s, 3H), 4.06 (s, 1H), 4.85 (dd, $J_1 = 17.4$ Hz, $J_2 = 1.2$ Hz, 1H), 5.06 (dd, $J_1 = 10.4$ Hz, $J_2 = 0.6$ Hz, 1H), 5.60-5.76 (m, 1H), 7.18-7.28 (m, 3H), 7.42 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 29.11, 52.20, 59.98, 74.51, 120.06, 123.26, 125.55, 126.97, 129.25, 131.48, 134.11, 146.75, 174.19; IR (neat, cm^{-1}): ν 700, 788, 929, 1174, 1199, 1331, 1715, 2953, 2980, 3504; MS (ESI) m/z 276.8 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_2$ ($\text{M}-\text{OH}$) $^+$ 237.0677. Found 237.0672; $[\alpha]_{\text{D}}^{23} = +56.7$ ($c = 1.30$, CHCl_3) for 82% ee.

(-)-Methyl 3-(3-chlorophenyl)-2-ethyl-3-hydroxybutanoate (12d-syn) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 0.72 (t, $J = 7.4$ Hz, 3H), 1.09-1.16 (m, 1H), 1.47 (s, 3H), 1.61-1.70 (m, 1H), 2.62 (dd, $J_1 = 11.3$ Hz, $J_2 = 3.7$ Hz, 1H), 3.763 (s, 1H), 3.77 (s, 3H), 7.18-7.26 (m, 3H), 7.44 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.08, 20.87, 30.18, 51.78, 57.34, 74.15, 123.00, 125.34, 126.88, 129.41, 134.20, 147.47, 176.98; IR (neat, cm^{-1}): ν 700, 787, 1176, 1200, 1361, 1713, 2933, 2968, 3508; MS (ESI) m/z 279.0 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{17}\text{ClO}_3$ (M) $^+$ 256.0866. Found 256.0860; $[\alpha]_{\text{D}}^{27} = -15.5$ ($c = 0.75$, CHCl_3) for 82% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 13.9$ min (major), 17.8 min (minor). $\lambda = 220\text{nm}$.

(+)-Methyl 3-hydroxy-3-methyl-5-phenyl-2-vinylpentanoate (7e) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 1.39 (s, 3H), 3.22 (d, $J = 9.2$ Hz, 1H), 3.65 (s, 1H), 3.71 (s, 3H), 5.18 (d, $J = 17.1$ Hz, 1H), 5.23 (d, $J = 10.4$ Hz, 1H), 5.88-5.96 (m, 1H), 6.16 (d, $J = 16.1$ Hz, 1H), 6.63 (d, $J = 16.1$ Hz,

1H), 7.18-7.36 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 27.31, 52.09, 59.98, 73.60, 119.98, 126.52, 127.52, 128.52, 128.91, 132.13, 132.80, 136.86, 173.85; IR (neat, cm^{-1}): ν 694, 749, 970, 1732, 2925, 3502; MS (ESI) m/z 269.1 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{17}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 229.1223. Found 229.1232; $[\alpha]_{\text{D}}^{27} = +22.7$ ($c = 0.60$, CHCl_3) for 67% ee;

(-)-Methyl 2-ethyl-3-hydroxy-3-methyl-5-phenylpentanoate (12e-syn) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 0.82 (t, $J = 7.3$ Hz, 3H), 1.20 (s, 3H), 1.61-1.75 (m, 3H), 1.75-1.85 (m, 1H), 2.35 (dd, $J_1 = 11.3$ Hz, $J_2 = 3.9$ Hz, 1H), 3.53 (td, $J_1 = 12.8$ Hz, $J_2 = 5.1$ Hz, 1H), 2.66 (td, $J_1 = 13.1$ Hz, $J_2 = 4.6$ Hz, 1H), 2.77 (s, 1H), 3.67 (s, 3H), 7.01-7.23 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.40, 20.12, 25.90, 29.95, 41.09, 51.47, 56.25, 72.69, 98.47, 125.86, 128.34, 142.17, 176.46; IR (neat, cm^{-1}): ν 700, 1168, 1196, 1731, 2966, 3513; MS (ESI) m/z 273.2 (M^++Na); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 233.1536. Found 233.1534; $[\alpha]_{\text{D}}^{28} = -10.9$ ($c = 0.97$, CHCl_3) for 67% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 25.4$ min (major), 32.3 min (minor). $\lambda = 220\text{nm}$.

(+)-Methyl 2-(1-hydroxy-1-(4-iodophenyl)ethyl)but-3-enoate (7j) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 1.64 (s, 3H), 3.46 (d, $J = 8.6$ Hz, 1H), 3.82 (s, 3H), 4.11 (s, 1H), 5.04 (d, $J = 17.1$ Hz, 1H), 5.14 (d, $J = 10.4$ Hz, 1H), 5.76-5.84 (m, 1H), 7.23 (d, $J = 7.0$ Hz, 2H), 7.73 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 29.10, 52.20, 59.94, 74.60, 92.43, 120.05, 127.25, 131.53, 137.06, 144.35, 174.18; IR (neat, cm^{-1}): ν 823, 926, 1004, 1173, 1199, 1715, 2925, 2951, 3506; MS (ESI) m/z 369.1 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{15}\text{IO}_3$ (M) $^+$ 346.0061. Found 346.0054; $[\alpha]_{\text{D}}^{27} = +34.4$ ($c = 1.26$, CHCl_3) for 84% ee; HPLC condition: Chiralcel OD-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 24.5$ min (major), 28.4 min (minor). $\lambda = 220\text{nm}$.

(+)-Methyl 2-(1-hydroxy-1-(naphthalene-2-yl)ethyl)but-3-enoate (7k) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 1.60 (s, 3H), 3.49 (d, $J = 8.5$ Hz, 1H), 3.66 (s, 3H), 4.07 (s, 1H), 4.87 (d, $J = 17.1$ Hz, 1H), 4.92 (d, $J = 10.1$ Hz, 1H), 5.66-5.73 (m, 1H), 7.35-7.45 (m, 3H), 7.71-7.77 (m, 3H), 7.86 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 29.55, 52.39, 60.14, 75.19, 119.92, 123.48, 124.28, 126.01, 126.22, 127.67, 127.92, 128.55, 132.07, 132.54, 133.36, 142.18, 174.67; IR (neat, cm^{-1}): ν 477, 749, 819, 927, 1173, 1197, 1329, 1714, 2951, 2977, 3504; MS (ESI) m/z 292.9 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2$ ($\text{M}-\text{OH}$) $^+$ 253.1223. Found 253.1236; $[\alpha]_{\text{D}}^{23} = +40.2$ ($c = 0.94$, CHCl_3) for 84% ee.

(-)-Methyl 2-ethyl-3-hydroxy-3-(naphthalene-2-yl)butanoate (12k-syn) (major isomer)

^1H NMR (500 MHz, CDCl_3) δ : 0.71 (t, $J = 7.6$ Hz, 3H), 1.12-1.20 (m, 1H), 1.58 (s, 3H), 1.65-1.75 (m, 1H), 2.79 (dd, $J_1 = 11.3$ Hz, $J_2 = 3.7$ Hz, 1H), 3.79 (s, 3H), 3.84 (s, 1H), 7.42-7.48 (m, 3H), 7.80 (d, $J = 8.9$ Hz, 2H), 7.84 (d, $J = 8.9$ Hz, 1H), 7.97 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.14, 20.98, 30.29, 51.73, 57.36, 74.66, 123.01, 123.81, 125.75, 126.04, 127.43, 127.83, 128.26, 132.25, 133.16, 142.73, 177.27; IR (neat, cm^{-1}): ν 478, 748, 818, 1174,

1198, 1712, 2966, 3507; MS (ESI) m/z 295.0 ($M+Na$)⁺; HRMS (EI) calcd for $C_{17}H_{20}O_3$ (M)⁺ 272.1407. Found 272.1420; $[\alpha]_D^{27} = -22.0$ ($c = 0.50$, $CHCl_3$) for 84% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.3 mL / min, n -hexane / i -PrOH = 199 / 1, $t = 29.3$ min (major), 39.9 min (minor). $\lambda = 254$ nm.

4-1. Absolute configuration determination for γ -cis selective aldol adduct **3a**

(+)-(*R*)-6-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (**13**)

The γ -cis selective aldol adduct **3a** was stirred overnight in AcOH under reflux and the corresponding lactone **13** was obtained in almost quantitative yield after purification via silica gel short column chromatography. 1H NMR (500 MHz, $CDCl_3$) δ : 1.71 (s, 3H), 2.78 (ddd, $J_1 = 18.6$ Hz, $J_2 = 3.5$ Hz, $J_3 = 2.3$ Hz, 1H), 2.95 (ddd, $J_1 = 18.6$ Hz, $J_2 = 5.2$ Hz, $J_3 = 1.6$ Hz, 1H), 5.99 (ddd, $J_1 = 9.8$ Hz, $J_2 = 2.3$ Hz, $J_3 = 1.6$ Hz, 1H), 6.73 (dd, $J_1 = 9.8$ Hz, $J_2 = 5.2$ Hz, $J_3 = 3.5$ Hz, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ : 30.13, 35.39, 82.47, 121.89, 124.50, 127.58, 128.54, 143.36, 143.91, 163.25; IR (neat, cm^{-1}): ν 1062, 1261, 1380, 1641, 1710, 2980; MS (ESI) m/z 211.1 ($M+Na$)⁺; $[\alpha]_D^{26} = +32.8$ ($c = 0.80$, $CHCl_3$) for 98% ee from (*R*)-Tol-BINAP, lit.⁵ $[\alpha]_D^{25} = -33.2$ ($c = 1.0$, $CHCl_3$) for 80% ee from (*S*)-Tol-BINAP; HPLC condition: Chiralpak AD column, flow rate: 1.0 mL / min, n -hexane / i -PrOH = 49 / 1, $t = 22.6$ min (minor), 34.4 min (major). $\lambda = 220$ nm. After comparison with the reported data of optical rotation,⁵ the absolute configuration of the γ -cis selective aldol adduct **3a** was determined to be *R*.

4-2. Absolute configuration determination for α -selective aldol adduct **7a**

The relative configurations of α -selective aldol adducts **7a** (both major and minor isomers) were determined after hydrogenation conversion to **12a** (*syn* and *anti*) through comparison with the reported NMR chemical shifts.⁴ The absolute configuration of major isomer **7a** was determined after conversion to compound **16** (Route 1), which can also be generated from the reported catalytic asymmetric allylation reaction of crotylborate to acetophenone⁶ followed by hydrogenation reduction (Route 2).

4-2-1. Route 1:

(-)-(2R, 3R)-Methyl 2-ethyl-3-hydroxy-3-phenylbutanoate (12a-syn)

The α -selective aldol adducts **7a** was treated with atmospheric H_2 in THF in the presence of catalytic Pd/C overnight. After filtration and evaporation, purification through silica gel column chromatography gave **12a-syn** in almost quantitative yield and the spectroscopic data have been shown in the above context. The ee value of **12a-syn** sample used for the determination of absolute configuration was 60%.

(+)-(2S, 3R)-2-ethyl-3-phenylbutane-1,3-diol (14)

To alcohol **12a-syn** (55.2 mg, 0.25 mmol) in THF at -78°C , DIBAL-H (1.55 mL, 1.5 mmol, 6.0 eq, 0.97 M in Hex) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. H_2O was carefully dropped to the mixture, and the products were extracted with EtOAc after simple filtration. The combined organic layer was washed with brine, and dried over Na_2SO_4 . The crude product was then purified through a short column chromatography (eluent: AcOEt /hexane = 1/5 to 1/2) to give diol **14** in 74% yield. ^1H NMR (500 MHz, CDCl_3) δ : 0.75 (t, $J = 7.3$ Hz, 3H), 1.13-1.19 (m, 2H), 1.57-1.62 (m, 4H), 3.65 (dd, $J_1 = 11.3$ Hz, $J_2 = 4.9$ Hz, 1H), 3.95 (dd, $J_1 = 11.3$ Hz, $J_2 = 2.7$ Hz, 1H), 7.15-7.33 (m, 5H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.68, 18.78, 29.20, 29.74, 51.07, 61.58, 67.72, 78.62, 107.98, 125.06, 126.51, 128.04, 146.91; IR (neat, cm^{-1}): ν 701, 762, 1446, 2359, 2929, 2964, 3336; MS (ESI) m/z 216.8 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M) $^+$ 194.1302. Found 194.1292; $[\alpha]_{\text{D}}^{22} = +22.7$ ($c = 1.42$, CHCl_3).

(+)-(2S, 3R)-2-ethyl-3-hydroxy-3-phenylbutyl 4-methylbenzensulfonate (15)

To diol **14** (28.4 mg, 0.15 mmol) in pyridine (0.5 mL), TsCl (37.2 mg, 0.19 mmol, 1.33 eq) was added at 0°C , and the mixture was warmed to room temperature and stirred overnight. H_2O was then added, and the product was extracted with AcOEt . The combined organic layer was washed with 20% aqueous CuSO_4 and brine, and then dried over Na_2SO_4 . Filtration, evaporation and purification through silica gel afforded tosylate **15** in 50% yield. ^1H NMR (500 MHz, CDCl_3) δ : 0.70 (t, $J = 7.7$ Hz, 3H), 1.16-1.25 (m, 1H), 1.33-1.41 (m, 1H), 1.50 (s, 3H), 1.80-1.87 (br, 2H), 2.44 (s, 3H), 4.00 (dd, $J_1 = 10.4$ Hz, $J_2 = 3.7$ Hz, 1H), 4.22 (dd, $J_1 = 10.4$ Hz, $J_2 = 4.9$ Hz, 1H), 7.17-7.34 (m, 7H), 7.75 (d, $J = 4.9$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 12.34, 19.31, 21.75, 28.47, 50.41, 69.58, 76.35, 124.91, 126.87, 128.08, 128.26, 129.96, 132.86, 144.96, 147.03; IR (neat, cm^{-1}): ν 554, 667, 702, 943, 1096, 1175, 1188, 1358, 2342, 2360, 2965, 3538; MS (ESI) m/z 370.9 ($\text{M}+\text{Na}$) $^+$; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{23}\text{O}_3\text{S}$ ($\text{M}-\text{OH}$) $^+$ 331.1362. Found 331.1379; $[\alpha]_{\text{D}}^{22} = +12.5$ ($c = 1.26$, CHCl_3).

(+)-(2*R*,3*R*)-3-methyl-2-phenylpentan-2-ol ((+)-**16**)

To lithium aluminum hydride (14.0 mg, 0.36 mmol, 5 eq), a solution of tosylate **10-syn** (25.2 mg, 0.072 mmol) in THF (1 mL) was added at room temperature. And the mixture was stirred under reflux for 1h. H₂O (15 μ L), 15% aqueous NaOH (15 μ L), and H₂O (45 μ L) were added successively. Filtration and evaporation gave product **11-anti** in 80% yield. ¹H NMR (500 MHz, CDCl₃) δ : 0.81-0.87 (m, 6H), 0.88-0.96 (m, 1H), 1.45-1.52 (m, 4H), 1.61 (br, 1H), 1.66-1.70 (m, 1H), 7.19-7.41 (m, 5H); ¹³C NMR (126 MHz, CDCl₃) δ : 12.70, 13.33, 23.95, 26.66, 45.82, 77.23, 125.24, 126.41, 127.92, 148.22; IR (neat, cm⁻¹): ν 700, 760, 1377, 1446, 2342, 2360, 2875, 2931, 2965, 3466; MS (ESI) m/z 200.8 (M+Na)⁺; HRMS (EI) calcd for C₁₂H₁₇ (M-OH)⁺ 161.1325. Found 161.1339; [α]_D²² = +20.0 (c = 1.02, CHCl₃).

4-2-2. Route 2:

(-)-(2*S*,3*S*)-3-methyl-2-phenylpent-4-en-2-ol (**17**)

According to the reported procedure by this group, the catalytic asymmetric allylation reaction of crotylboronate to acetophenone was performed to give the corresponding tertiary alcohols in 48% yield (85% ee) for **17-syn** isomer and in 52% yield (89% ee) for **17-anti** isomer, respectively.⁶ Both diastereomers are separable through medium pressure silica gel column (eluent: AcOEt/hexane = 1/50 to 1/15). And the spectroscopic data for intermediate **17-anti** is shown below. ¹H NMR (500 MHz, CDCl₃) δ : 0.96 (d, J = 6.9 Hz, 3H), 1.52 (s, 3H), 1.99 (s, 1H), 2.59 (quintet, J = 6.9 Hz, 1H), 5.10 (m, 2H), 5.70 (m, 1H), 7.23 (m, 1H), 7.33 (t, J = 7.5 Hz, 2H), 7.42 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 14.07, 25.83, 48.73, 75.66, 116.6, 125.4, 126.6, 127.9, 139.9, 147.0; [α]_D²³ = -83.1 (c = 0.64, CHCl₃) for 89% ee, lit.⁶: [α]_D²² = -72.8 (c = 1.05, CHCl₃) for 85% ee; HPLC condition: Chiralpak AS-H column, flow rate: 0.8 mL / min, *n*-hexane / *i*-PrOH = 99 / 1, t = 7.5 min (minor), 7.9 min (major). λ = 220nm.

(-)-(2*S*,3*S*)-3-methyl-2-phenylpentan-2-ol ((-)-**16**)

The crotylated product **17-anti** was treated with atmospheric H₂ in THF in the presence of catalytic Pd/C overnight. After filtration and evaporation, partial purification through silica gel column chromatography gave the corresponding tertiary alcohol **16** in quantitative yield and other spectroscopic data has been shown in the above context except [α]_D²² = -11.6 (c = 0.45, CHCl₃).

Based on comparison of optical rotation signs of **16** samples prepared from different routes mentioned above, the absolute configuration of major α -selective aldol adduct **7a** was determined to be *R,R*.

5. Procedure for the conversion of α -aldolate via cross metathesis followed by hydrogenation reaction;

7a (20.0 mg, 0.1 mmol, 81% ee) was subjected to cross metathesis reaction using excess amount of 4-phenyl-1-butene (0.5 mmol, 5 eq.) in the presence of 20 mol% of Grubbs 2nd catalyst in dichloromethane under the concentration of 1.0 M on **7a**. The reaction mixture was then refluxed at 40 °C for overnight and then cooled down to room temperature. After silica gel column chromatography, the cross metathesis product was obtained in over 90% yield. The following hydrogenation reaction was performed using 10 mol% of Pd/C catalyst under ambient pressure of hydrogen in THF for overnight. The target conversion was completed in 66% yield to generate only one isomer with 81% ee.

(+)-(2*R*,3*R*)-2-(1-Hydroxy-1-phenyl-ethyl)-6-phenyl-hexanoic acid methyl ester (8): ¹H NMR (500 MHz, CDCl₃) δ : 0.98-1.11 (m, 3H), 1.36-1.44 (m, 2H), 1.43 (s, 3H), 1.61-1.68 (m, 1H), 2.33-2.40 (m, 2H), 2.68 (dd, $J_1 = 11.6$ Hz, $J_2 = 3.1$ Hz, 1H), 3.59 (s, 1H), 3.66 (s, 3H), 6.96-7.36 (m, 10H); ¹³C NMR (126 MHz, CDCl₃) δ : 27.04, 27.18, 30.20, 30.74, 35.34, 51.64, 55.59, 74.44, 124.73, 125.54, 126.65, 128.10, 128.13, 128.28, 142.24, 145.21, 177.19; IR (neat, cm⁻¹): ν 700, 1199, 1447, 1712, 2931, 3512; MS (ESI) m/z 349.1 (M+Na)⁺; HRMS (FAB) calcd for C₂₁H₂₅O₂ (M-OH)⁺ 309.1849. Found 309.1857; $[\alpha]_D^{25} = +3.2$ ($c = 1.10$, CHCl₃) for 81% ee; HPLC condition: Chiralcel OD-H column, flow rate: 0.5 mL / min, *n*-hexane / *i*-PrOH = 199 / 1, $t = 38.5$ min (major), 54.5 min (minor). $\lambda = 220$ nm.

6. General procedure for the catalytic alkylative aldol reaction to ketones using dialkylzinc

A catalyst solution was generated from CuOAc (0.01 mmol, 5.0 mol%) and (*R*)-DTBM-SEGPHOS (0.012 mmol, 6.0 mol%) in degassed THF (0.25 mL) under stirring at room temperature for 10 min. Ethyl 2,3-butadienoate (0.3 mmol, 1.5 equiv.) and acetophenone (0.2 mmol) were then added successively to the catalyst solution. Another 10 min later, dialkylzinc (1.0 M in hexane, 0.32 mmol, 1.6 equiv.) was added slowly to the reaction mixture via syringe pump for 2 h at 0 degree. The mixture was allowed to stir at 0 degree for further 14 h. MeOH was added to quench the reaction; the generated precipitate was filtered off over Celite pad. After evaporation of solvent, the nmr yield was determined by nmr analysis of the crude product with DMF as an internal standard. Purification by preparative thin layer column chromatography (eluent: AcOEt/hexane = 1/7) gave the pure lactone **9** or **10** for spectroscopic data and enantiomeric excess determination by HPLC analysis.

4,6-Dimethyl-6-phenyl-5,6-dihydro-pyran-2-one (9)

^1H NMR (500 MHz, CDCl_3) δ : 1.70 (s, 3H), 1.92 (s, 3H), 3.00 (dd, $J_1 = 14.0$ Hz, $J_2 = 8.0$ Hz, 1H), 2.74 (d, $J = 17.7$ Hz, 1H), 2.83 (d, $J = 17.7$ Hz, 1H), 5.78 (s, 1H), 7.23-7.30 (m, 1H), 7.31-7.40 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ : 23.17, 30.13, 40.49, 82.41, 116.83, 124.22, 127.51, 128.53, 144.08, 155.27, 164.71; IR (neat, cm^{-1}): ν 848, 1141, 1261, 1445, 1708, 2979; MS (ESI) m/z 225.0 ($\text{M}+\text{Na}$) $^+$; HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 203.1067. Found 203.1060; $[\alpha]_{\text{D}}^{26} = -7.9$ ($c = 0.33$, CHCl_3) for 88% ee; HPLC condition: Chiralpak OJ-H column, flow rate: 1.0 mL / min, n -hexane / i -PrOH = 20 / 1, $t = 22.9$ min (minor), 25.3 min (minor). $\lambda = 220\text{nm}$. Absolute configuration was not determined at this stage.

4-Ethyl-6-methyl-6-phenyl-5,6-dihydro-pyran-2-one (10)

^1H NMR (500 MHz, CDCl_3) δ : 1.05 (t, $J = 7.6$ Hz, 3H), 1.70 (s, 3H), 2.15-2.25 (m, 2H), 2.73 (d, $J = 17.7$ Hz, 1H), 2.84 (d, $J = 17.7$ Hz, 1H), 5.76 (s, 1H), 7.23-7.30 (m, 1H), 7.31-7.40 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ : 10.49, 29.74, 30.04, 39.39, 82.31, 114.93, 124.27, 127.47, 128.49, 144.07, 160.24, 164.99; IR (neat, cm^{-1}): ν 865, 1140, 1262, 1712, 2975.; MS (ESI) m/z 239.0 ($\text{M}+\text{Na}$) $^+$; HRMS (FAB) calcd for $\text{C}_{14}\text{H}_{17}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 217.1223. Found 217.1222; $[\alpha]_{\text{D}}^{26} = +2.2$ ($c = 0.27$, CHCl_3) for 77% ee; HPLC condition: Chiralpak OJ-H column, flow rate: 0.5 mL / min, n -hexane / i -PrOH = 20 / 1, $t = 34.3$ min (major), 40.6 min (minor). $\lambda = 220\text{nm}$. Absolute configuration was not determined at this stage.

7. References:

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