Supporting Information

A New Method for Catalytic Aldol Reaction to Ketones

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General: NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ¹H NMR, 125.65 MHz for ¹³C NMR, and 470.4 MHz for ¹⁹F NMR. Chemical shifts were reported downfield from TMS (= 0) for ¹H NMR. For ¹³C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ¹⁹F NMR were carried out with trifluoroacetic acid (= -79 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 or GC 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 254 nm; mobile phase, hexane-2-propanol. GC analysis was performed on Shimadzu GC-14A with Varian Chrasil DEX CB column (0.25 mm x 25 m). In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Normal glassware can be used to conduct the reactions in this manuscript. CuF•3PPh₃•2EtOH was synthesized following the reported procedure.¹ (EtO)₃SiF was purchased from Azmax Co. Ltd. (Fax: +81-436-20-2665) and used after distillation. Synthesis of **1j** will be reported in elsewhere. Briefly, methyl- α -D-glucopyranoside was selectively converted to the 6-membered benzylidene acetal (PhCH(OMe)₂, cat. *p*-TsOH, DMF, 79%), which was subjected to a mono-MOM protection of the diol (Bu₂SnO; MOMCl, Et₃N, toluene, 55%, 1:1 inseparable constitutional isomer). The Swern oxidation of the mixture followed by separation through silica gel column chromatography gave **1j** (43% yield): ¹H NMR (500 MHz, CDCl₃) δ : 3.44 (s, 3H), 3.48 (s, 3H), 3.93 (dd, *J* = 10.4, 10.4 Hz, 1H), 4.10 (ddd, *J* = 4.6, 10.1, 10.1 Hz, 1H), 4.28 (dd, *J* = 1.3, 9.8 Hz, 1H), 4.43 (m, 2H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.80 (d, *J* = 7.1 Hz, 1H), 5.20 (d, *J* = 4.6 Hz, 1H), 5.56 (s, 1H), 7.36 (m, 3H), 7.51 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 55.61, 56.14, 65.41, 69.47, 78.37, 82.23, 96.59, 102.00, 102.71, 126.40, 128.29, 129.36, 136.29, 195.36; IR (neat, cm⁻¹) 1748; MS *m/z* 324 (M⁺), 293 (M⁺-OMe); HRMS Calcd for C₁₆H₂₀O₇ (M⁺) 324.1209. Found 324.1208.

A typical procedure for ketene silyl acetal synthesis (synthesis of **2a):** Ketene silyl acetals were synthesized using a modified Corey's internal quench method.² To a solution of ⁱPr₂NH (47.8 mL, 34 g, 341 mmol) in THF (330 mL), BuLi (1.56 M solution in hexane, 200 mL, 312 mmol) was added dropwise in an ice bath, and the whole was stirred for 15 min. After cooling to -78 °C, a mixture of AcOEt (27.7 mL, 25g, 284 mmol) and TMSCl (43.5 mL, 37 g, 343 mmol) in THF (170 mL) was added. After the addition was completed, the cooling bath was removed, and the mixture was stirred for 3 h at rt. Then, THF was evaporated and hexane was added. The resulting precipitate was filtrated off through a celite pad, and the residue was washed with hexane. The combined filtrate was evaporated, and the resulting residue was purified by distillation (bp. 70 °C/60 mmHg), giving **2a** in 42% yield (19 g), which contains a trace amount of C-TMS (less than 1/50). *E*-Ketene silyl acetals **2c**, **2e**, and *E*-**2g** were synthesized using the same procedure. *Z*-Ketene silyl acetals **2d** and *Z*-**2g** were prepared through deprotonation by LDA in the presence of HMPA (25% v/v to THF) followed by the trap with TMSCl. Ketene silyl acetal **2f** is commercially available.

ketene silyl acetal	b. p.	yield	¹ H NMR (in C ₆ D ₆)
2a	70 °C (60 mmHg)	42%	0.25 (s, 9H), 0.95 (t, <i>J</i> = 7.2 Hz, 3H), 3.17 (d, <i>J</i> = 2.5 Hz, 1H), 3.42 (q, <i>J</i> = 7.2 Hz, 2H), 3.59 (d, <i>J</i> = 2.5 Hz, 1H)
2b	41-42 °C (30 mmHg)	34%	0.20 (s, 9H), 3.10 (d, <i>J</i> = 2.5 Hz, 1H), 3.13 (s, 3H), 3.47 (d, <i>J</i> = 2.5 Hz, 1H)

35–36 °C (15 mmHg)	54%	0.12 (s, 9H), 1.69 (d, $J = 6.4$ Hz, 3H), 3.35 (s, 3H), 3.79 (q, $J = 6.4$ Hz, 2H)
52–57 °C (40 mmHg)	34%	0.21 (s, 9H), 1.72 (d, $J = 6.5$ Hz, 3H), 3.11 (s, 3H), 3.45 (q, $J = 6.5$ Hz, 1H)
50–60 °C (35 mmHg)	76%	0.18 (s, 9H), 2.34 (dt, $J = 2.1, 8.9$ Hz, 2H), 3.79 (t, $J = 2.1$ Hz, 1H), 3.99 (t, $J = 8.9$ Hz, 2H)
85–95 °C (0.07 mmHg)	80%	0.20 (s, 9H), 3.33 (s, 3H), 3.53 (d like, $J = 7.7$ Hz, 2H), 4.02 (t, $J = 7.7$ Hz, 1H), 7.15 (m, 1H), 7.19 (t, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.7$ Hz, 2H)
77–82 °C (0.06 mmHg)	42%	0.20 (s, 9H), 3.06 (s, 3H), 3.26 (d, $J = 8.0$ Hz, 1H), 3.52 (d, $J = 8.0$ Hz, 1H), 3.65 (t, $J = 8.0$ Hz, 1H), 7.09 (m, 1H), 7.22 (t, $J = 7.8$ Hz, 2H), 7.30 (d, $J = 7.7$ Hz, 2H)
70–73 °C (6 mmHg)	85%	1.00 (t, $J = 7.0$ Hz, 3H), 1.17 (t, $J = 7.0$ Hz, 9H), 3.24 (d, $J = 2.8$ Hz, 1H), 3.46 (q, $J = 7.0$ Hz, 2H), 3.80 (d, $J = 2.8$ Hz, 1H), 3.92 (q, $J = 7.0$ Hz, 6H)

General procedure for the aldol reaction to ketones: A ketone (0.40 mmol), $(\text{EtO})_3\text{SiF}$ (89 μL , 0.48 mmol, 1.2 equiv), and a ketene silyl acetal (0.80 mmol, 2 equiv) were added successively to a solution of $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}$ (9.6 mg, 0.01 mmol, 2.5 mol %) at room temperature in degassed THF (0.6 mL). After the ketone completely disappeared on TLC analysis (reaction period shown in Table 1), $3\text{HF}\cdot \text{NEt}_3$ (0.3 mL) was added. The product was extracted with AcOEt and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4 . Filtration, evaporation, and purification by silica gel column chromatography (eluent: AcOEt/hexane = 1/10) gave the pure aldol product. Aldol products **3aa**, **3ca**, **3da**, **3ea**, **3fa**, and **3ia** were reported by Denmark.³ The stereochemistry of **3ac** and **3ad** (the same compound) was determined by the comparison of the ^1H NMR with the reported NMR charts.⁴ **3ca**⁵ and **3af**⁶ are known compounds. Spectroscopic data of new aldol products are as follows.

3-Hydroxy-3-methyloctanoic acid ethyl ester (3ga): ^1H NMR (500 MHz, CDCl_3) δ : 0.89 (t, $J = 7.0$ Hz, 3 H), 1.23 (s, 3H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.3 (m, 6H), 1.50 (m, 2H), 2.43 (d, $J = 15.6$ Hz, 1H), 2.50 (d, $J = 15.6$ Hz, 1H), 3.54 (s, 1H), 4.18 (q, $J = 7.2$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 13.92, 14.10, 22.51, 23.55, 26.58, 32.19, 41.98, 44.75, 60.49, 70.93, 173.03; IR (neat, cm^{-1}) 3522, 1716; MS m/z 203 ($\text{M}^+ + 1$), 187 ($\text{M}^+ - \text{CH}_3$), 185 ($\text{M}^+ - \text{OH}$); HRMS Calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$ ($\text{M}^+ - \text{CH}_3$) 187.1329. Found 187.1328.

3-Hydroxy-3-methyldec-4-enoic acid ethyl ester (3ha): ^1H NMR (500 MHz, CDCl_3) δ : 0.88 (t, $J = 7.0$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.31 (s, 3H), 1.3 (m, 6H), 2.00 (q like, $J = 6.7$ Hz, 2H), 2.52 (d, $J = 15.6$ Hz, 1H), 2.56 (d, $J = 15.6$ Hz, 1H), 3.87 (s, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 5.52 (d, $J = 15.6$ Hz, 1H), 5.66 (dt, $J = 15.6$ Hz, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 13.96, 14.11, 22.44, 28.35, 28.85, 31.21, 32.00, 45.59, 60.53, 70.76, 128.82, 135.04, 172.60; IR (neat, cm^{-1}) 3520, 1717; MS m/z 228 (M^+), 213 ($\text{M}^+ - \text{CH}_3$), 210 ($\text{M}^+ - \text{H}_2\text{O}$); HRMS Calcd for $\text{C}_{12}\text{H}_{21}\text{O}_3$ ($\text{M}^+ - \text{CH}_3$) 213.1485. Found 213.1480.

(8-Hydroxy-6-methoxy-7-methoxymethoxy-2-phenylhexahydro-pyrano[3,2-

d][1,3]dioxin-8-yl)-acetic acid methyl ester (3jb): Based on the NOE measurement, the product via equatorial attack of methyl acetate was obtained as the major isomer (ca.

15:1). ^1H NMR (500 MHz, CDCl_3) δ : 2.82 (d, $J = 15.6$ Hz, 1H), 2.90 (d, $J = 15.6$ Hz, 1H), 3.43 (s, 3H), 3.49 (s, 3H), 3.63 (s, 3H), 3.74 (d, $J = 9.5$ Hz, 1H), 3.76 (dd, $J = 10.4$, 10.4 Hz, 1H), 3.89 (d, $J = 3.7$ Hz, 1H), 3.95 (s, 1H), 4.14 (ddd, $J = 5.2$ Hz, 10.4, 10.4 Hz, 1H), 4.36 (dd, $J = 5.2$, 10.4 Hz, 1H), 4.76 (s like, 2H), 4.96 (d, $J = 3.7$ Hz, 1H), 5.53 (s, 1H), 7.34 (m, 3H), 7.49 (m, 2H); ^{13}C

NMR (126 MHz, CDCl₃) δ : 36.48, 51.58, 55.81, 55.92, 58.92, 69.07, 73.19, 75.91, 79.21, 97.76, 100.38, 101.72, 126.22, 128.11, 128.94, 137.22, 171.52; IR (neat, cm⁻¹) 3502, 1731; MS *m/z* 398 (M⁺), 367 (M⁺-OMe), 353 (M⁺-CH₂OMe). No aldol reaction proceeded in the presence of 10 mol % Sc(OTf)₃ in CH₂Cl₂ at room temperature⁷ for over 30 h (a small amount of PhCHO was produced due to a partial hydrolysis of the benzylidene acetal).

3-Benzyl-3-hydroxy-2-methyl-4-phenylbutyric acid methyl ester (3kc): ¹H NMR (500 MHz, CDCl₃) δ : 1.30 (d, *J* = 7.0 Hz, 3H), 2.55 (q, *J* = 7.0 Hz, 1H), 2.76 (d, *J* = 14.0 Hz, 1H), 2.79 (d, *J* = 14.0 Hz, 1H), 2.84 (d, *J* = 14.0 Hz, 1H), 3.07 (d, *J* = 14.0 Hz, 1H), 3.49 (s, 1H), 3.54 (s, 3H), 5.26 (m, 10H); ¹³C NMR (126 MHz, CDCl₃) δ : 12.66, 42.55, 43.52, 45.16, 51.67, 75.53, 126.46, 128.04, 130.71, 130.91, 136.77, 136.96, 176.19; IR (neat, cm⁻¹) 1732; MS *m/z* 299 (M⁺+1), 280 (M⁺-H₂O); HRMS Calcd for C₁₉H₂₀O₂ (M⁺-H₂O) 280.1463. Found 280.1451.

3-(1-Ethyl-1-hydroxypropyl)-dihydrofuran-2-one (3le): ¹H NMR (500 MHz, CDCl₃) δ : 0.93 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 1.54 (m, 3H), 1.80 (m, 1H), 2.19 (m, 1H), 2.28 (m, 1H), 2.82 (dd, *J* = 9.2, 11.0 Hz, 1H), 3.15 (s, 1H), 4.20 (ddd, *J* = 7.0, 9.5, 9.5 Hz, 1H), 4.37 (ddd, *J* = 2.8, 9.5, 9.5 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ : 7.40, 7.64, 24.59, 28.60, 28.76, 45.95, 66.38, 74.54, 179.40; IR (neat, cm⁻¹) 3502, 1759; MS *m/z* 154 (M⁺-H₂O), 143 (M⁺-Et); HRMS Calcd for C₉H₁₄O₂ (M⁺-H₂O) 154.0994. Found 154.0991.

Effect of (EtO)₃SiF [comparison between the reactions in the absence/presence of (EtO)₃SiF]: The following results clearly show the beneficial effect of additive (EtO)₃SiF.

entry	ketone	(EtO) ₃ SiF	Time (h)	Yield (%)
1	1a	+	2	95
2		-	12	66
3	1e	+	4	90
4		-	45	< 30
5	1f	+	4	85
6		-	48	48
7	1g	+	1	88
8		-	74	28
9	1h	+	1	88
10		-	8.5	70
11	1i	+	3.5	85
12		-	31	82

Kinetic experiments to determine the order dependency of the initial reaction rate on catalyst concentration and ketene silyl acetal concentration:

Initial kinetics was measured by ¹H NMR, observing the increase of the methyl signal on triethoxysilyl group of the aldol product with a various catalyst or ketene silyl acetal concentrations (see the following scheme).

Determination of the Order Dependency on Catalyst Concentration

The order dependency of the reaction rate on the catalyst was determined by the slope of log k –log [CuF] graph (right).

Determination of the Order Dependency on Silyl Ketene Acetal Concentration

The order dependency of the reaction rate on the ketene silyl acetal was determined by the slope of log k –log [ketene acetal] graph (right).

Catalytic enantioselective aldol reaction of **2g to ketone **1l**:** A solution of CuF•3PPh₃•2EtOH (9.6 mg, 0.010 mmol, 2.5 mol %) and (*S*)-tol-BINAP (13.6 mg, 0.020 mmol, 5 mol %) in degassed THF (0.3 mL) was stirred at room temperature for 30 min. To this pale yellow solution, ketone **1l** (42 μ L, 0.40 mmol) and (EtO)₃SiF (89 μ L, 0.48 mmol, 1.2 equiv) were added at –20 °C and stirred for 15 min. Ketene silyl acetal *E*-**2g** was then added at –20 °C and the mixture was stirred for 24 h. 3HF•NEt₃ (0.3 mL) was added to quench the reaction, and the mixture was stirred at room temperature for 30 min. After the addition of satd. NaCl, the product was extracted with AcOEt/hexane = 1/1, and the combined organic layer was washed with satd. NaHCO₃. Drying with Na₂SO₄, filtration, concentration, and purification by silica gel column chromatography (AcOEt/hexane = 1/15) gave aldol product **3lg** in 99% yield as colorless oil (100 mg). Ee was determined by chiral GC analysis to be 82% from *E*-enolate and 80% ee from *Z*-enolate.

2-Benzyl-3-ethyl-3-hydroxypentanoic acid methyl ester (3lg**):** ¹H NMR (500 MHz, CDCl₃) δ : 0.92 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H), 1.47 (m, 2H), 1.60 (m, 1H), 1.72 (m, 1H), 2.80 (dd, J = 4.6, 11.3 Hz, 1H), 2.97 (m, 2H), 3.03 (s, 1H), 3.44 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ : 7.62, 7.65, 26.51, 30.15, 33.03, 51.21, 54.07, 74.91, 126.26, 128.30, 128.72, 139.21, 176.27; IR (neat, cm^{–1}) 1713; [α]_D²⁴ –42.4 (c 1.61, CHCl₃) (80% ee); MS m/z 232 (M⁺–H₂O), 221 (M⁺–Et); HRMS Calcd for C₁₅H₂₀O₂ (M⁺–H₂O) 232.1463.

Found 232.1464; GC (Varian, Chirasil DEX CB (0.25 mm x 25 m), Column temperature = 130 °C (isothermal), Injector temperature = 200 °C, Detector temperature = 200 °C, Inlet pressure = 1.3 kg/cm²), $t_r(\text{minor})$ = 74.8 min, $t_r(\text{major})$ = 76.1 min.

Determination of absolute configuration: The absolute configuration of **3lg** was determined after conversion to **13** and by comparison of the sign of the optical rotation (Scheme 3).

Scheme 3

(2S)-2-Benzyl-3-ethyl-3-hydroxypentanoic acid (12): To a solution of **3lg** (20 mg, 0.080 mmol) in DMF (0.3 mL), PhSH (41 μ L, 0.40 mmol, 5 equiv) and Cs₂CO₃ (117 mg, 0.36 mmol, 4.5 equiv) were added at room temperature and the mixture was stirred at 90 °C for 1 h.⁸ Satd. NaHCO₃ was added and the aqueous layer was washed with Et₂O. The aqueous layer was acidified with 1 M HCl to pH 1, which was extracted with AcOEt. The combine organic layer was washed with satd. NaCl and dried over Na₂SO₄. Filtration, evaporation, and partial purification through silica gel column chromatography gave **12** in 79% yield (15 mg). ¹H NMR (500 MHz, CDCl₃) δ : 0.90 (t, J = 7.7 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H), 1.57 (m, 3H), 1.72 (m, 1H), 2.81 (br t, J = 7.7 Hz, 1H), 2.96 (m, 2H), 7.16 (d, J = 7.4 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 7.26 (t, J = 7.4 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 7.65, 7.68, 26.76, 30.02, 32.86, 53.99, 75.29, 126.48, 128.48, 128.79, 138.88, 180.03.

(2S)-2-Benzyl-5,5-diethyl-oxazolin-2-one (13): Et₃N (11 μ L, 0.076 mmol, 1.2 equiv) and DPPA (15 μ L, 0.069 mmol, 1.1 equiv) were added to a solution of **12** (15 mg, 0.063 mmol) in toluene (0.3 mL) at room temperature, and the mixture was stirred at 90 °C for 7 h.⁹ H₂O was added and the product was extracted with CH₂Cl₂. The combined organic layer was washed with satd. NaHCO₃ and satd. NaCl, and dried over Na₂SO₄. Filtration, evaporation, and purification through silica gel column chromatography gave **13** in 48% yield as colorless oil (7 mg). ¹H NMR (500 MHz, CDCl₃) δ : 0.97 (t, J = 7.4 Hz, 3H), 1.06 (t, J = 7.3 Hz, 3H), 1.71 (m, 1H), 1.80 (q, J = 7.4 Hz, 2H), 1.93 (m, 1H), 2.70 (dd, J = 11.3, 13.1 Hz, 1H), 2.84 (dd, J = 3.4, 13.1 Hz, 1H), 3.76 (dd, J = 3.4, 11.3 Hz, 1H), 4.92 (s, 1H), 7.18 (d, J = 7.4 Hz, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.34 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ : 7.49, 7.76, 24.98, 29.13, 37.21, 61.02, 87.32, 127.13, 128.83, 129.04, 137.15, 157.90; IR (neat, cm⁻¹) 1748; MS m/z 233 (M⁺), 204 (M⁺-Et); HRMS Calcd for C₁₄H₁₉NO₂ (M⁺) 233.1416. Found 233.1413; $[\alpha]_D^{20}$ -64.2 (c 0.33, CHCl₃) (80% ee). The absolute configuration was determined based on the sign of the optical rotation (see below).

Conversion of L-phenylalanine methyl ester hydrochloride (L-Phe-OMe·HCl) to oxazolin-2-one 13:¹⁰

To an EtMgBr (13.1 mmol, 6 equiv) solution in ether (14.4 mL), L-Phe-OMe·HCl (470 mg, 2.18 mmol) was added in an ice bath, and the mixture was stirred at room temperature for 2 h. Cooling in an ice bath, H₂O was added and the product was extracted with ether. The combined organic layer was washed with satd. NaCl and dried over Na₂SO₄. Filtration and evaporation gave the crude amino alcohol (448 mg). To a solution of the amino alcohol (50 mg, 0.24 mmol) in CH₂Cl₂ (0.5 mL), 1,1'-carbonyldiimidazole (CDI, 47 mg, 0.29 mmol, 1.2 equiv) was added, and the mixture was stirred under reflux for 2 h. 1 M HCl was added and the product was extracted with CH₂Cl₂. The combined organic layer was washed with satd. NaCl and dried over Na₂SO₄. Filtration, evaporation, and purification through silica gel column chromatography gave **13** in 56% yield for 2 steps (32 mg). $[\alpha]_D^{23}$ -72.6 (c 1.46, CHCl₃).

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