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Supporting Material

Highly Regioselective Alkylation at the More Hindered α -Site of Unsymmetrical Ketones by the Combined Use of Aluminum Tris(2,6-diphenylphenoxide)(ATPH) and LDA [MS# JA963274O-22-315]

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General Methods. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^1H NMR spectra were measured on Varian Gemini-300 (300 MHz) at ambient temperature. Data are recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, and m = multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were recorded on Varian gemini-300 (75 MHz) spectrometer at ambient temperature. Chemical shifts are recorded in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard (deutero chloroform at 77.07 ppm). Gas chromatography spectral data were obtained with a Shimadzu GC-8A gas chromatograph using a capillary column of PEG-HT (0.25 x 25000 mm, Gasukuro Kogyo Inc.). HPLC analysis was performed using a Shimadzu LC-10AD equipped with a Shimadzu SPD-M10A detector and a Wakosil 5SIL column (4.0 x 2500 mm, Wako). All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC Plates (silica gel 60 GF254 0.25 mm) was used. The products were purified by preparative column chromatography on silica gel (E. Merck Art. 9385). Microanalysis were accomplished at the Faculty of Agriculture, Nagoya University.

General Procedure for Alkylation of Unsymmetrical Ketones by the Combined Use of ATPH and LDA. ATPH was prepared as described in Ref. 4 in the text. To a solution of ATPH (1.1 equiv) in toluene (5.0 mL) was added 2-

methylcyclohexanone (**1a**) (61 μ L, 0.50 mmol) at -78 $^{\circ}$ C under argon atmosphere, followed by a transfer of a THF (5.0 mL) solution of LDA, prepared from diisopropylamine (77 μ L, 0.55 mmol) and a 1.60 M hexane solution of *n*-BuLi (0.34 mL, 0.55 mmol) at -78 $^{\circ}$ C for 30 min, by a steel cannula. After stirring at -78 $^{\circ}$ C for 1 h, to the mixture was added MeOTf (566 μ L, 5.0 mmol) dropwise, and the mixture was maintained at this temperature for 7.5 h, poured into 1N HCl, and was extracted with ether. The organic layer was dried over Na_2SO_4 , and concentrated by rotary evaporator. Residue was purified by column chromatography on silica gel (CH_2Cl_2 /pentane = 1/1 as eluent) to give 33 mg of a mixture of 2,2-dimethylcyclohexanone (**2a**) and 2,6-dimethylcyclohexanone (**3a**) (53%) as a colorless oil. The ratio of **2a** and **3a** was determined by GC-analysis. retention times: $t_R = 26.6$ min for **2a** and $t_R = 27.8$ and 30.5 min for *cis*- and *trans*-**3a** at a column temperature of 60 $^{\circ}$ C at a carrier gas pressure of 0.4 kg/cm². **2a** and **3a** are commercially available from Aldrich.

2-methyl-2-octylcyclohexanone (**2b**) IR (neat) 2930, 2857, 1709, 1466, 1377, 1312, 1125, 986 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.46-2.27 (m, 2H), 1.96-1.21 (m, 20H), 1.03 (s, 3H), 0.88 (t, 3H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 216.2, 48.6, 39.4, 38.8, 37.5, 31.8, 30.3, 29.4, 29.2, 27.5, 23.7, 22.6, 22.5, 21.0, 14.1; Anal. Calcd for $\text{C}_{15}\text{H}_{28}\text{O}$: C, 80.29, H, 12.58. Found, C, 80.39, H, 12.56. The isomeric ratio of **2b** and a regioisomer 2-methyl-6-octylcyclohexanone (**3b**) was determined by HPLC analysis: retention times: $t_R = 13.5$ min for **2b** and $t_R = 11.3$ min and 12.5 min for *cis* and *trans* **3b** using hexane-*i*-PrOH (100 : 1) as eluent at a flow rate of 0.25 mL/min and UV detection at 280 nm. *cis*-**3b**: IR (neat) 2928, 2857, 1713, 1456, 1377, 1316, 1129, 1071, 982, 855, 722 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.00 (d, 3H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 214.5, 50.9, 45.7, 37.5, 35.2, 31.9, 29.9, 29.5, 29.3, 29.1, 27.3, 25.6, 22.7, 14.6, 14.1. *trans*-**3b**: IR (neat) 2928, 2857, 1709, 1458, 1377, 1341, 1314, 1219, 1123, 1082, 997, 723 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.05 (d, 3H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 216.9, 49.5, 42.2, 35.6, 32.3, 31.8, 30.9, 29.6, 29.4, 29.2, 27.3, 22.6,

20.5, 15.3, 14.1; The mixture of *cis*- and *trans*-**3b**: Anal. Calcd for C₁₅H₂₈O: C, 80.29, H, 12.58. Found, C, 80.39, H, 12.56.

2-allyl-2-methylcyclohexanone (**2c**) is a known compound.¹ The ratio of **2c** and a stereomixture of 2-allyl-6-methylcyclohexanone (**3c**) was determined by GC-analysis: retention times: $t_R = 46.4$ min for **2c** and $t_R = 43.2$ min and 47.7 min for *cis* and *trans* **3c** at a column temperature of 60 °C at a carrier gas pressure of 0.6 kg/cm². *Cis*- and *trans*-**3c** are also known compounds.²

2-methyl-2-(2-propynyl)cyclohexanone (**2d**) IR (neat) 3293, 2936, 2867, 1709, 1426, 1377, 1314, 1129, 1076, 733 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.53-2.31 (m, 4H), 2.00 (t, 1H, $J = 2.9$ Hz), 1.99-1.72 (m, 6H), 1.23 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 214.0, 81.1, 70.7, 47.9, 38.5, 37.9, 27.6, 27.3, 22.4, 21.2; Anal. Calcd for C₁₀H₁₄O: C, 79.96, H, 9.39. Found, C, 79.95, H, 9.50. The isomeric ratio of **2d** and a stereomixture of 2-methyl-6-(2-propynyl)cyclohexanone (**3d**) was determined by ¹H NMR analysis. *cis*-**3d**: IR (neat) 3295, 2969, 2934, 2861, 1713, 1451, 1428, 1377, 1130, 995, 916, 853 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.03 (d, 3H, $J = 6.5$ Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 212.1, 82.8, 69.2, 49.5, 45.4, 37.1, 34.2, 25.2, 18.8, 14.4; *trans*-**3d**: IR (neat) 3308, 2971, 2936, 2867, 1709, 1456, 1429, 1377, 1132, 914, 852, 735 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.15 (d, 3H, $J = 7.1$ Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 214.5, 82.1, 69.7, 46.2, 43.6, 33.9, 32.1, 19.9, 19.3, 16.3. The mixture of *cis*- and *trans*-**3d**: Anal. Calcd for C₁₀H₁₄O: C, 79.96, H, 9.39. Found, C, 79.80, H, 9.58.

2-methyl-2-octylcyclopentanone (**2e**) IR (neat) 2959, 2928, 2857, 1738, 1408, 1375, 1161, 1067 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.35-2.14 (m, 2H), 1.96-1.66 (m, 4H), 1.41-1.19 (m, 14H), 0.99 (s, 3H, C(2)CH₃), 0.88 (t, 3H, $J = 6.7$ Hz, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 223.8, 48.3, 37.7, 36.6, 35.6, 31.8, 30.2, 29.4, 29.2, 24.2, 22.6, 21.8, 18.7, 14.1; Anal. Calcd for C₁₄H₂₆O: C, 79.94, H, 12.46. Found, C, 79.95, H, 12.45. The regioisomeric ratio of **2e** and a stereomixture of 2-methyl-5-octylcyclopentanone (**3e**) was determined by ¹H NMR analysis. *cis*-**3e**: IR (neat) 2959, 2928, 2857, 1736, 1456, 1374, 1335, 1161, 1105, 909, 725 cm⁻¹; ¹H NMR (300

MHz, CDCl₃) δ 1.06 (d, 3H, *J* = 7.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 223.6, 48.1, 42.9, 31.8, 30.3, 29.6, 29.4, 29.3, 29.1, 27.7, 26.4, 22.6, 15.1, 14.1; *trans*-**3e**: IR (neat) 2959, 2928, 2857, 1738, 1456, 1374, 1339, 1157, 911, 723 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.11 (d, 3H, *J* = 6.9 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 223.0, 48.9, 44.3, 31.8, 30.3, 30.0, 29.6, 29.4, 29.2, 27.6, 27.4, 22.6, 14.4, 14.1. The mixture of *cis*- and *trans*-**3e**: Anal. Calcd for C₁₄H₂₆O: C, 79.94, H, 12.46. Found, C, 79.79, H, 12.77. The relative stereochemistry of *cis*- and *trans*-**3e** was established according to the ¹H and ¹³C NMR values of structurally related other 2,5-dialkylcyclopentanones.³

2-allyl-2-methylcyclopentanone (**2f**) is a known compound.⁴ The ratio of **2f** and a stereomixture of 2-allyl-5-methylcyclopentanone (**3f**) was determined by GC-analysis: retention times: *t_R* = 19.6 min for **2f** and *t_R* = 20.7 min and 21.5 min for *cis*- and *trans*-**3f** at a column temperature of 60 °C at a carrier gas pressure of 0.6 kg/cm². *Cis*- and *trans*-**3f** are prepared as described in the literature procedure.⁵

3-methyl-2-undecanone (**2g**) is a known compound.⁶ The ratio of **2g** and a regioisomer 3-dodecanone (**3g**) was determined by GC-analysis: retention times: *t_R* = 27.1 min for **2g** and *t_R* = 36.4 min for **3g** at a column temperature of 80 °C at a carrier gas pressure of 0.6 kg/cm². Regioisomer **3g** is also a known compound.⁷

3-butyl-2-undecanone (**2h**) IR (neat) 2957, 2928, 2872, 2857, 1715, 1466, 1377, 1352, 1165, 1136, 947, 918, 723 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.46-2.37 (m, 1H), 2.11 (s, 3H), 1.65-1.16 (m, 20H), 0.88 (t, 6H, *J* = 7.1 Hz, 2x CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 213.1, 53.3, 31.8, 31.7, 31.4, 29.7, 29.6, 29.4, 29.2, 28.6, 27.4, 22.7, 22.6, 14.0, 13.8; Anal. Calcd for C₁₅H₃₀O: C, 79.58, H, 13.36. Found, C, 79.56, H, 13.40. The isomeric ratio of **2h** and a regioisomer 6-pentadecanone (**3h**) was determined by ¹H NMR analysis. **3h**: IR (neat) 2928, 2857, 1717, 1466, 1410, 1377, 1134, 1075, 723 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.38 (t, 4H, *J* = 7.5 Hz, CH₂COCH₂); ¹³C NMR (75 MHz, CDCl₃) δ 211.7, 42.8, 42.7, 31.8, 31.4, 29.4, 29.2, 23.9, 23.5, 22.6, 22.4, 14.1, 13.9; Anal. Calcd for C₁₅H₃₀O: C, 79.58, H, 13.36. Found, C, 79.41, H, 13.65.

3,3-dimethyl-2-undecanone (**2i**) IR (neat) 3854, 2959, 2928, 2857, 1709, 1470, 1387, 1354, 1136, 959 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 2.11 (s, 3H, COCH_3), 1.52-1.47 (m, 2H), 1.34-1.10 (m, 12H), 1.10 (s, 6H, $\text{C}(3)(\text{CH}_3)_2$), 0.88 (t, 3H, $J = 6.7$ Hz, CH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 214.2, 47.8, 40.1, 31.8, 30.2, 29.4, 29.2, 25.0, 24.7, 24.3, 22.6, 14.1; Anal. Calcd for $\text{C}_{13}\text{H}_{26}\text{O}$: C, 78.72, H, 13.21. Found, C, 78.71, H, 13.21. The isomeric ratio of **2i** and a regioisomer 2-methyl-3-dodecanone (**3i**) was determined by GC analysis. retention times: $t_R = 13.3$ min for **2i** and $t_R = 16.2$ min for **3i** at a column temperature of 100 $^\circ\text{C}$ at a carrier gas pressure of 0.6 kg/cm^2 . Regioisomer **3i** was prepared as in the literature procedure.⁸

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