



Supporting Information

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69451 Weinheim, Germany

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Enantioselective Cu-catalyzed 1,4-Addition of Various Grignard Reagents to Cyclohexenone using Taddol-derived Phosphine-Phosphite Ligands and 2-Methyl-THF as a Solvent

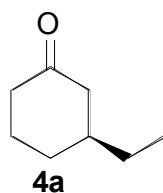
*Tobias Robert, Janna Velder, and Hans-Günther Schmalz**

General experimental information. All reactions were carried out under an inert argon atmosphere and in heated glassware using standard Schlenk techniques. Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl. NMR spectra were measured on a Bruker instrument (Avance II 600) at 600 MHz for ^1H and 150 MHz for ^{13}C . Deuterated chloroform was used as a solvent. Proton shifts are reported in ppm (δ) downfielded from TMS and were determined by reference to the residual solvent peak (CHCl_3 , 7.24 ppm for hydrogen atoms, 77.0 ppm for carbon atoms). Reactions were monitored by GC-MS using an Agilent Technologies Model GC 6890N gas chromatograph coupled with an HP 5973N series mass selective detector and an HP 7683 GC autosampler was employed for all analyses. Samples were separated on a 30-m x 0.25-mm, HP-5 MS column. Enantiomeric excesses were determined by GC analysis using an Agilent Technologies Model GC 6890N gas chromatograph with a BGB 176 SE column (30m x 0.25mm), 6-TBDMS-2,3-Me- β -CD column (25m x 0.25mm) or Lipodex A column (50m x 0.25mm). Mass spectrometer MAT 900S (Finnigan) was used for DIP-MS mass spectra. Infrared spectra were recorded on a Paragon 100 FT IR instrument (Perkin-Elmer). Optical rotations were measured with a Perkin-Elmer 343 polarimeter, concentrations c are given in g/100 ml. The absolute configuration was determined in CH_3CN using a Jasco J-180 CD-spectropolarimeter, concentrations c are given in mg/ml. Grignard solutions were either synthesized from the corresponding alkylbromides or purchased from Chemetall in 2-Me-THF.

General procedure I (1,4-addition on an analytical scale): The Cu-salt (0.04 eq, 6 μmol) and the respective ligand (0.06 eq, 9 μmol) were dissolved in 1 ml of solvent and stirred for 15 min at r.t. under argon. After addition of enone **3** (1.0 eq, 150 μmol) the mixture was cooled (as specified in the Tables) and a dilute (0.1-0.5 mol/l) solution of the Grignard reagent (1.0 eq, 150 μmol) was slowly added by means of a syringe. The reaction mixture was then stirred for another 15 min and quenched by addition of MeOH (1 ml) and 1M aqueous NH_4Cl solution (2 ml). The organic layer was filtered through a short pad of silica and analyzed by chiral gas chromatography.

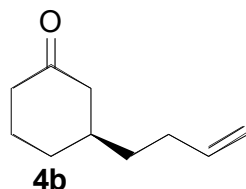
General procedure II: (1,4-addition on a preparative scale): CuBr-SMe₂ (0.05 eq, 0.45 mmol) and the ligand (0.06 eq, 0.54 mmol) were dissolved in 15 ml of solvent and stirred for 15 min at r.t. After addition of enone **3** (1.0 eq, 9 mmol) the reaction mixture was cooled to -78 °C and a dilute (0.1-0.5 mol/l) solution of the Grignard reagent (1.2 eq, 10.8 mmol) was slowly added over 2 h by means of a syringe pump. The mixture was then stirred for another 30 min and quenched by addition of MeOH (5 ml) and 1M aqueous NH₄Cl solution (10 ml). The layers were separated and the aqueous phase was extracted with tert-butylmethylether. The combined organic were washed with brine, dried over MgSO₄ and the solvent was evaporated in vacuo. The crude products (yellowish oils) were purified by distillation (0.2 mbar) and subsequent flash chromatography (cyclohex/EtOAc = 10:1) to give the pure 1,4-addition products **4** as colorless oils.

(S)-3-Ethyl-cyclohexanone (4a)



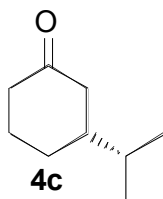
According to general procedure II, 93 mg (0.05 eq, 0.45 mmol) of CuBr-SMe₂, 478 mg (0.06 eq, 0.54 mmol) of ligand **7f** and 0.87 ml (9 mmol) of 2-cyclohexenone (**3**) in 15 ml of 2-Me-THF were reacted with a solution of ethyl magnesium bromide (10.8 mmol) in 18 ml of 2-MeTHF to give 680 mg (60%) of the product **4a** (90% ee). MW (C₈H₁₄O): 126.20; TLC (cyclohex/EtOAc = 5 /1): 0.39; ¹H NMR (600 MHz, CDCl₃): δ [ppm] = 0.88 (t, ³J_{HH} = 7.5 Hz, 3H, CH₃), 1.25-1.40 (m, 3H), 1.56-1.68 (m, 2H), 1.85-1.90 (m, 1H), 1.97 (Ψt, J = 12.7 Hz, 1H), 1.99-2.04 (m, 1H), 2.19-2.26 (m, 1H), 2.30-2.35 (m, 1H), 2.37-2.42 (m, 1H); ¹³C-NMR (150 MHz, CDCl₃): δ [ppm] = 11.2 (CH₃), 25.3 (CH₂), 39.3 (CH₂), 30.9 (CH₂), 40.8 (CH), 41.5 (CH₂), 47.9 (CH₂), 212.2 (Cq); FT-IR (ATR): $\tilde{\nu}$ [cm⁻¹] = 2931, (vs), 2862 (s), 1713 (vs), 1456 (s), 1418 (m), 1381 (w), 1344 (m), 1250 (m), 1224 (m), 1196 (m), 1125 (m), 1074 (m), 1033 (s), 1013 (s), 966 (s), 913 (w), 868 (m), 817 (w), 769 (w); DIP-MS (EI, 70 eV): m/z (%) = 126 (30, [M]⁺), 97 (70, [C₆H₉O]⁺), 83 (17), 70 (31), 69 (23), 55 (49). Chiral GC analysis (BGB 176 SE, initial temp. 40°C, rate 0.2 °C/min, final temp. 63 °C), retention times: 100.8 min (major) / 104.7 min (minor); [α]_x (20 °C, CH₂Cl₂, c = 1.50 g/100 ml): [α]₅₈₉: -9.0; [α]₅₄₆: -11.9; [α]₄₀₅: -48.2; [α]₃₆₅: -96.4; [α]₃₃₄: -220.0; CD: Θ (γ) = -90.50 (292.3 nm), (c = 0.51 mg/ml in CH₃CN).

(*R*)-3-But-3-enyl-cyclohexanone (4b)



According to general procedure II, 93 mg (0.05 eq, 0.45 mmol) of CuBr-SMe₂, 478 mg (0.06 eq, 0.54 mmol) of ligand **7f** and 0.87 ml (9 mmol) of 2-cyclohexenone (**3**) in 15 ml of Et₂O were reacted with a solution of 3-butenyl magnesium bromide (13.5 mmol) in 15 ml of Et₂O to give 971 mg (71%) of the product **4b** (91% ee). MW (C₁₀H₁₆O): 152.23; TLC (cyclohex/EtOAc = 5 /1) : 0.33; ¹H NMR (600 MHz, CDCl₃): δ [ppm] = 1.27-1.47 (m, 3H), 1.57-1.66 (m, 1H), 1.73-1.82 (m, 1H), 1.88 (Ψd, *J* = 13.3 Hz, 1H), 1.95-2.08 (m, 4H), 2.19-2.27 (m, 1H), 2.29-2.36 (m, 1H), 2.40 (Ψd, *J* = 13.8 Hz, 1H), 4.93 (d, ³*J*_{HH} = 10.2 Hz, 1H, =CH₂), 4.98 (d, ³*J*_{HH} = 17.1 Hz, 1H, =CH₂), 5.71-5.78 (m, 1H, =CH); ¹³C NMR (150 MHz, CDCl₃): δ [ppm] = 25.2 (CH₂), 30.8 (CH₂), 31.2 (CH₂), 35.7 (CH₂), 38.4 (CH), 41.5 (CH₂), 48.0 (CH₂), 114.8 (=CH₂), 138.2 (=CH), 211.8 (C=O); FT-IR (ATR): $\tilde{\nu}$ [cm⁻¹] = 3072 (w), 2922 (s), 2848 (m), 1714 (vs), 1639 (m), 1447 (s), 1418 (m), 1345 (m), 1313 (m), 1278 (w), 1223 (s), 1056 (w), 993 (w), 909 (s), 865 (w), 751 (w); DIP-MS (EI, 70 eV): *m/z* (%) = 152 (6, [M]⁺), 137 (5), 123 (10), 110 (38), 97 (100, [C₆H₉O]⁺), 82 (36), 81 (46), 69 (24), 67 (54), 55 (49). Chiral GC analysis (6-TBDMS-2,3-Me-β-CD, initial temp. 50°C, rate 1 °C/min, final temp. 90 °C); retention times : 54.7 min (major) / 56.5 min (minor); [α]_λ (20 °C, CH₂Cl₂, *c* = 0.46 g/100 ml): [α]₅₈₉: -15.0; [α]₅₄₆: -21.0; [α]₄₀₅: -89.9; [α]₃₆₅: -179.8; [α]₃₃₄: -442.3; CD : Θ (γ) = -48.19 (292.7 nm), (*c* = 0.29 mg/ml in CH₃CN).

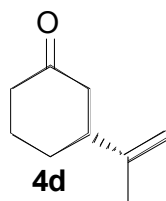
(*R*)-3-*i*-Propyl-cyclohexanone (4c)



According to general procedure II, 93 mg (0.05 eq, 0.45 mmol) of CuBr-SMe₂, 478 mg (0.06 eq, 0.54 mmol) of ligand **7f** and 0.87 ml (9 mmol) of 2-cyclohexenone (**3**) in 15 ml of 2-Me-THF were reacted with a solution of *i*-propyl magnesium bromide (13.5 mmol) in 15 ml of Et₂O to give 1109 mg (88%) of the product **4b** (82% ee). MW (C₉H₁₆O): 140.22; TLC (cyclohex/EtOAc = 5 /1): 0.33; ¹H NMR (600 MHz, CDCl₃): δ [ppm] = 0.87 (Ψt, *J* = 6.2 Hz, 6H, CH₃), 1.29-1.38 (m, 1H), 1.50-

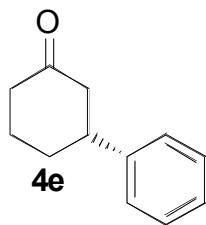
1.62 (m, 3H), 1.83 (Ψ d, $J = 13.3$ Hz, 1H), 2.01-2.08 (m, 2H), 2.17-2.25 (m, 1H), 2.33 (Ψ t, $J = 14.6$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ [ppm] = 19.3 (CH_3), 19.5 (CH_3), 25.5 (CH_2), 28.3 (CH_2), 32.5 (CH), 41.5 (CH_2), 45.3 (CH_2), 45.4 (CH), 212.6 ($\text{C}=\text{O}$); FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2956 (vs), 2929 (s), 2870 (s), 1713 (vs), 1465 (m), 1447 (m), 1423 (m), 1386 (m), 1368 (m), 1345 (w), 1313 (m), 1257 (m), 1225 (m), 1196 (w), 1121 (w), 1057 (w), 1015 (w), 901 (w), 870 (w), 754 (w); DIP-MS (EI, 70 eV): m/z (%) = 140 (18, $[\text{M}]^+$), 97 (100, $[\text{C}_6\text{H}_9\text{O}]^+$), 82 (20), 69 (49), 55 (37). Chiral GC analysis (6-TBDMS-2,3-Me- β -CD, initial temp. 40 $^\circ\text{C}$, initial time 10 min, rate 1 $^\circ\text{C}/\text{min}$, final temp. 80 $^\circ\text{C}$); retention times : 52.8. min (minor) / 53.2 min (major); $[\alpha]_\lambda$ (20 $^\circ\text{C}$, CH_2Cl_2 , $c = 0.77$ g/100 ml): $[\alpha]_{589}$: +15.2; $[\alpha]_{546}$: +20.2; $[\alpha]_{405}$: +81.0; $[\alpha]_{365}$: +162.9; $[\alpha]_{334}$: +397.2; CD : Θ (γ) = 47.63 (291.5 nm), ($c = 0.33$ mg/ml in CH_3CN).

(*R*)-3-*i*-Propenyl-cyclohexanone (4d)



According to general procedure II, 93 mg (0.05 eq, 0.45 mmol) of $\text{CuBr}\cdot\text{SMe}_2$, 478 mg (0.06 eq, 0.54 mmol) of ligand **7f** and 0.87 ml (9 mmol) of 2-cyclohexenone (**3**) in 15 ml of 2-Me-THF were reacted with a solution of *i*-propenyl magnesium bromide (13.5 mmol) in 15 ml of 2-Me-THF to give 609 mg (49%) of the product **4b** (92% ee). MW ($\text{C}_9\text{H}_{14}\text{O}$): 138.21; TLC (cyclohex/EtOAc = 5 /1): 0.35; ^1H NMR (600 MHz, CDCl_3): δ [ppm] = 1.53-1.60 (m, 1H), 1.60-1.70 (m, 1H), 1.72 (s, 3H, CH_3), 1.91 (Ψ d, $J = 13.0$ Hz, 1H), 2.02-2.07 (m, 1H), 2.23-2.30 (m, 2H), 2.32-2.44 (m, 3H), 4.70 (s, 1H), 4.76 (s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ [ppm] = 20.6 (CH_3), 25.1 (CH_2), 30.0 (CH_2), 41.3 (CH_2), 45.7 (CH), 46.7(CH_2), 110.0 ($=\text{CH}_2$), 147.5 ($\text{C}=\text{CH}_2$), 211.5 ($\text{C}=\text{O}$) FT-IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3073 (w), 2937 (s), 2863 (m), 1713 (vs), 1644 (m), 1447 (s), 1375 (w), 1344 (w), 1314 (m), 1270 (w), 1250 (w), 1222 s), 1181 (w), 1100 (w), 1056 (w), 951 (w), 892 (s), 753 (w); DIP-MS (EI, 70 eV): m/z (%) = 138 (12, $[\text{M}]^+$), 123 (24), 110 (9), 95 (100), 82 (29), 81 (36), 69 (25), 68 (36), 67 (91), 55 (22). Chiral GC analysis (Lipodex A, initial temp. 50 $^\circ\text{C}$, initial time 15 min, rate 1 $^\circ\text{C}/\text{min}$, final temp. 100 $^\circ\text{C}$); retention times : 47.9 min (major) / 48.9 min (minor); $[\alpha]_\lambda$ (20 $^\circ\text{C}$, CH_2Cl_2 , $c = 0.68$ g/100 ml): $[\alpha]_{589}$: +16.0; $[\alpha]_{546}$: +22.4; $[\alpha]_{405}$: +116.2; $[\alpha]_{365}$: +256.5; $[\alpha]_{334}$: +696.1; CD : Θ (γ) = 98.14 (292.8 nm), ($c = 0.57$ mg/ml in CH_3CN).

(R)-3-Phenyl-cyclohexanone (4e)



According to general procedure II, 93 mg (0.05 eq, 0.45 mmol) of CuBr-SMe₂, 478 mg (0.06 eq, 0.54 mmol) of ligand **7f** and 0.87 ml (9 mmol) of 2-cyclohexenone (**3**) in 15 ml of 2-Me-THF were reacted with a solution of phenyl magnesium bromide (10.8 mmol) in 18 ml of 2-Me-THF to give xx mg (50%) of the product **4b** (92% ee). MW (C₁₂H₁₄O): 174.239; TLC (cyclohex/EtOAc = 5 /1): 0.25; ¹H NMR (600 MHz, CDCl₃): δ [ppm] = 1.72-1.81 (m, 1H, CH₂), 1.81-1.88 (m, 1H, CH₂), 2.04-2.09 (m, 1H, CH₂), 2.11-2.16 (m, 1H, CH₂), 2.33-2.39 (m, 1H, CH₂), 2.42-2.47 (m, 1H, CH₂), 2.48-2.54 (m, 1H, CH₂), 2.55-2.60 (m, 1H, CH₂), 2.99 (tt, *J*_A = 11.8 Hz, *J*_B = 3.8 Hz, 1H, CH), 7.18-7.24 (m, 3H, CH), 7.31 (Ψt, *J* = 7.5 Hz, 2H, CH); ¹³C NMR (150 MHz, CDCl₃): δ [ppm] = 25.5 (CH₂), 32.7 (CH₂), 41.2 (CH₂), 44.7 (CH), 48.9 (CH₂), 126.5 (2C, CH), 126.7 (CH), 128.7 (2C, CH), 144.3 (Cq), 211.0 (Cq); FT-IR (ATR): $\tilde{\nu}$ [cm⁻¹] = 3058 (w), 3026 (w), 2934 (s), 2861 (m), 1711 (vs), 1602 (w), 1495 (m), 1450 (s), 1428 (m), 1343 (w), 1313 (m), 1248 (m), 1221 (s), 1181 (w), 1098 (w), 1068 (w), 1030 (m), 971 (m), 916 (w), 880 (w), 795 (w), 754 (s), 699 (s), 652 (w); DIP-MS (EI, 70 eV): *m/z* (%) = 174 (53, [M]⁺), 131 (63), 117 (100), 104 (95), 103 (44), 91 (34), 78 (24), 77 (22). Chiral GC analysis (6-TBDMS-2,3-Me-β-CD, initial temp. 100 °C, initial time 10 min, rate 1 °C/min, final temp. 170 °C); retention times : 43.7 min (minor) / 44.5 min (major); [α]_λ (20 °C, CH₂Cl₂, c = 0.84 g/100 ml): [α]₅₈₉: +18.3; [α]₅₄₆: +26.1; [α]₄₀₅: +147.3; [α]₃₆₅: +339.4; [α]₃₃₄: +979.0; CD : Θ (γ) = 59.35 (291.9 nm), (c = 0.38 mg/ml in CH₃CN).