Novel Carbon-Carbon Bond Formation Reaction of Methoxyallene Oxide Promoted by TiI_4

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Experimental Section

General Aspects

Infrared spectra were determined on a JASCO IR-810 spectrometer. ^{1}H NMR spectra were recorded with a JEOL EX-270 spectrometer using tetramethylsilane as an internal standard. High performance liquid chromatography (HPLC) was carried out on a Hitachi L-4000 detector and a Hitachi L-6000 pump using a Kanto Chemicals Mightysil column (*n*-hexane : ethyl acetate = 2 : 1 as an eluent). Dichloromethane was distilled from phosphorous pentoxide. Purification of products was performed by preparative TLC on silica gel Merck Kisel Gel PF254.

The reaction of methoxyallene oxide with acetals.

1,2-Dimethoxy-1-phenylbutan-3-one.

To a suspension of mCPBA (124.3 mg, 0.72 mmol) and salicylic acid (24.9 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of methoxyallene (50.5 mg, 0.72 mmol) in CH_2Cl_2 (1.0 mL) at 0 ˚C under an argon atmosphere, and the resulting mixture was stirred for 30 min at 0 ˚C. CH_2Cl_2 (1.0 mL) was added to TiI_4 (400 mg, 0.72 mmol) at ambient temperature under an argon atmosphere. The TiI_4 solution was stirred at ambient temperature for 10 min, and to it was added a solution of benzaldehyde dimethylacetal (54.8 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL) at -78 ˚C. The suspension of the crude reaction mixture derived from the epoxidation was transferred to the solution of titanium iodide and acetal with the aid of CH_2Cl_2 (1.5 mL). After being stirred at -78˚C to -20˚C, the reaction was quenched with sat. aqueous $NaHCO_3$, 5% aqueous $NaHSO_3$, and triethylamine. The mixture was filtered through a Celite pad and extracted with ethyl acetate (10 mLx3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC on silica gel (*n*-hexane : ethyl acetate = 3 : 1 as an eluent) gave 2-methoxy-1-(2-propyloxy)-1-phenylbutan-3-one (60.8 mg, 81%).

^{1}H NMR ($CDCl_3$) δ 2.11 (s, 0.84H), 2.20 (s, 2.16H), 3.22 (s, 0.84H), 3.23 (s, 2.16H), 3.24 (s, 2.16H), 3.28 (s, 0.84H), 3.64 (d, *J* = 3.63Hz, 0.72H), 3.74 (d, *J* = 6.59Hz, 0.28H), 4.34 (d, *J* = 6.59Hz, 0.28H), 4.51 (d, *J* = 3.63Hz, 0.72H), 7.28-7.38 (m, 5H).

IR (neat) 2900, 2800, 1730, 1460, 1360, 1200, 1105, 760, 700 cm^{-1}

1-Ethoxy-2-methoxy-1-phenylbutan-3-one.

^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.09Hz, 3H), 2.14 (s, 0.72H), 2.24 (s, 2.28H), 3.19 (s, 2.28H), 3.25 (s, 0.72H), 3.27-3.57 (m, 2H), 3.63 (d, *J* = 3.3Hz, 0.76H), 3.73 (d, *J* = 6.6 Hz, 0.24H), 4.44 (d, *J* = 6.6Hz, 0.24H), 4.62 (d, *J* = 3.3Hz, 0.76H), 7.27-7.42 (m, 5H).
IR (neat) 2950, 2850, 1730, 1460, 1360, 1220, 1105, 770, 705 cm^{-1}

1-(4-Chlorophenyl)-1,2-dimethoxybutan-3-one.
^{1}H NMR ($CDCl_3$) δ 2.12 (s, 0.72H), 2.23 (s, 2.28H), 3.21 (s, 0.72H), 3.22 (s, 2.28H), 3.23 (s, 2.28H), 3.29 (s, 0.72H), 3.58 (d, *J* = 3.3Hz, 0.76H), 3.70 (d, *J* = 6.43Hz, 0.24H), 4.33 (d, *J* = 6.43Hz, 0.24H), 4.50 (d, *J* = 3.3Hz, 0.76H), 7.25-7.38 (m, 4H).
IR (neat) 2970, 2910, 2800, 1730, 1500, 1420, 1360, 1210, 1105, 1030, 840 cm^{-1}

1,2-Dimethoxy-1-(4-methylphenyl)butan-3-one.
^{1}H NMR ($CDCl_3$) δ 2.12 (s, 0.66H), 2.20 (s, 2.34H), 2.35 (s, 3H), 3.20 (s, 0.66H), 3.22 (s, 2.34H), 3.25 (s, 2.34H), 3.27 (s, 0.66H), 3.63 (d, *J* = 3.63Hz, 0.78H), 3.73 (d, *J* = 6.6Hz, 0.22H), 4.31 (d, *J* = 6.6Hz, 0.22H), 4.46 (d, *J* = 6.6Hz, 0.78H), 7.16-7.20 (m, 2H), 7.24-7.30 (m, 2H).
IR (neat) 2950, 2900, 1730, 1520, 1460, 1360, 1190, 1100, 950, 820 cm^{-1}

The reaction of methoxyallene oxide with benzaldehyde dimethylacetal using TiI_4-Ti(O*i*-Pr)$_4$.

2-Methoxy-1-(2-propyloxy)-1-phenylbutan-3-one.
To a suspension of mCPBA (124.3 mg, 0.72 mmol) and salicylic acid (24.9 mg, 0.18 mmol) in CH_2Cl_2 (0.5 mL)was added a solution of methoxyallene (50.5 mg, 0.72 mmol) in CH_2Cl_2 (1.0 mL) at 0 ˚C under an argon atmosphere, and the resulting mixture was stirred for 30 min at 0 ˚C. To a solution of TiI_4 (200 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of Ti(O*i*-Pr)$_4$ (1.0 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) at 0 ˚C. The resulting solution was stirred at ambient temperature for 10 min, and to it was added a solution of benzaldehyde dimethylacetal (54.8 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL) at -78 ˚C. The suspension of the epoxidation reaction mixture was transferred to the solution of TiX_4 and acetal with the aid of CH_2Cl_2 (1.5 mL). After being stirred at -78˚C to -20˚C, the reaction was quenched with sat. aqueous $NaHCO_3$, 5% aqueous $NaHSO_3$, and triethylamine. The mixture was filtered through a Celite pad and extracted with ethyl acetate (10 mLx3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC on silica gel (*n*-hexane : ethyl acetate = 3 : 1 as an eluent) gave 2-methoxy-1-(2-propyloxy)-1-phenylbutan-3-one (25.7 mg, 30%).
^{1}H NMR ($CDCl_3$) δ 1.06 (d, *J* = 5.94Hz, 3H), 1.10 (d, *J* = 5.94Hz, 3H), 2.16 (s, 0.18H), 2.26 (s, 2.82H), 3.17 (s, 2.82H), 3.22 (s, 0.18H), 3.46 (m, 1H), 3.60 (d, *J* = 2.97Hz, 0.94H), 3.69 (d, *J* = 6.93H, 0.06H), 4.53 (d, *J* = 6.93Hz, 0.06H), 4.73 (d, *J* = 2.97Hz, 0.94H), 7.26-7.43 (m, 5H)
IR (neat) 2950, 1720, 1460, 1360, 1118, 1095, 1075, 710 cm^{-1}

The reaction of methoxyallene oxide with aldehydes.

1-Hydroxy-2-methoxy-1-phenylbutan-3-one.

To a suspension of mCPBA (124.3 mg, 0.72 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of methoxyallene (50.5 mg, 0.72 mmol) in CH_2Cl_2 (1.0 mL) at 0 ˚C under an argon atmosphere, and the resulting mixture was stirred for 30 min at 0 ˚C. To a solution of TiI_4 (300 mg, 0.54 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of Ti(O*i*-Pr)$_4$ (1.0 M in CH_2Cl_2, 0.54 mL, 0.54 mmol) at 0 ˚C. The resulting solution was stirred at ambient temperature for 10 min, and to it was added a solution of benzaldehyde (38.2 mg, 0.36 mmol) in CH_2Cl_2 (1.0 mL) at -78 ˚C. The suspension of the epoxidation reaction mixture was transferred to the solution of TiX_4 and aldehyde with the aid of CH_2Cl_2 (1.5 mL). After being stirred at -78˚C to -20˚C, the reaction was quenched with sat. aqueous $NaHCO_3$, 5% aqueous $NaHSO_3$, and triethylamine. The mixture was filtered through a Celite pad and extracted with ethyl acetate (10 mLx3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC on silica gel (*n*-hexane : ethyl acetate = 2 : 1 as an eluent) gave 1-hydroxy-2-methoxy-1-phenylbutan-2-one (50.2 mg, 72%).

^{1}H NMR ($CDCl_3$) δ 2.05 (s, 2.7H), 2.07 (s, 0.3H), 3.03 (d, *J* = 4.29Hz, 1H), 3.29 (s, 2.7H), 3.33 (s, 0.3H), 3.76 (d, *J* = 6.27 Hz, 1H), 4.88 (dd, *J* = 4.29 and 6.27Hz, 1H), 7.29-7.38 (m, 5H).

IR (neat) 3400, 3000, 2900, 1720, 1460, 1360, 1200, 1120, 700 cm^{-1}

1-Hydroxy-2-methoxy-1-(4-methoxyphenyl)butan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.05 (s, 0.75H), 2.06 (s, 2.25H), 2.90 (d, *J* = 3.96Hz, 0.75H), 2.98 (d, *J* = 4.95Hz, 0.25H), 3.31 (s, 2.25H), 3.36 (s, 0.75H), 3.73 (d, *J* = 6.59Hz, 1H), 3.80 (s, 3H), 4.81-4.85 (m, 1H), 6.88 (d, *J* = 8.41Hz, 2H), 7.28 (d, *J* = 8.41Hz, 2H).

IR (neat) 3400, 2900, 1720, 1630, 1520, 1260, 1120, 850, 560 cm^{-1}

1-(4-Bromophenyl)-1-hydroxy-2-methoxybutan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.09 (s, 2.85H), 2.12 (s, 0.15H), 3.10 (brs, 1H), 3.30 (s, 2.85H), 3.34 (s, 0.15H), 3.68 (d, *J* = 6.27Hz, 1H), 4.84 (brd, *J* = 5.28Hz, 1H), 7.24 (d, *J* = 8.58Hz, 2H), 7.47 (d, *J* = 8.58Hz, 2H).

IR (neat) 3400, 2900, 1720, 1500, 1360, 1200, 1130, 1080, 1020, 840, 530 cm^{-1}

1-(4-chlorophenyl)-1-hydroxy-2-methoxybutan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.09 (s, 2.82H), 2.11 (s, 0.18H), 3.17 (d, *J* = 4.29Hz, 1H), 3.29 (s, 2.82H), 3.34 (s, 0.18H), 3.69 (d, *J* = 6.27Hz, 1H), 4.85 (dd, *J* = 4.29 and 6.27Hz, 1H), 7.27-7.34 (m, 4H).

IR (neat) 3400, 2970, 2900, 1730, 1500, 1420, 1370, 1230, 1200, 1130, 1100, 1030, 850, 800, 750, 570 cm^{-1}

1-(4-Fluorophenyl)-1-hydroxy-2-methoxybutan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.07 (brs, 1H), 3.30 (s, 2.88H), 3.36 (s, 0.12H), 3.70 (d, *J* = 6.27Hz, 1H), 4.86 (d, *J* = 6.27Hz, 1H), 7.00-7.06 (m, 2H), 7.27-7.36 (m, 2H).

IR (neat) 3400, 2900, 2800, 1720, 1615, 1520, 1370, 1240, 1130, 860, 580 cm^{-1}

1-Hydroxy-2-methoxy-1-(4-nitrophenyl)butan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.16 (s, 2.82H), 2.20 (s, 0.18H), 3.32 (s, 3H), 3.35 (d, *J* = 4.29Hz, 1H), 3.71 (d, *J* = 6.27Hz, 1H), 5.02 (dd, *J* = 3.96 and 6.27Hz, 1H), 7.56 (d, *J* = 8.75Hz, 2H), 8.20 (d, *J* = 8.75Hz, 2H).

IR (neat) 3450, 2900, 2800, 1750, 1615, 1540, 1360, 1120, 865, 700 cm^{-1}

1-(2,6-dichlorophenyl)-1-Hydroxy-2-methoxybutan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.09 (s, 2.82H), 2.12 (s, 0.18H), 3.15 (brs, 1H), 3.30 (s, 2.82H), 3.34 (s, 0.18H), 3.68 (d, *J* = 6.27Hz, 1H), 4.84 (brd, *J* = 5.28Hz, 1H), 7.24 (d, *J* = 8.58Hz, 2H), 7.47 (d, *J* = 8.58Hz, 2H).

IR ($CHCl_3$) 3470, 2920, 2800, 1730, 1575, 1450, 1370, 1200, 1120, 1100 cm^{-1}

1-Hydroxy-2-methoxy-1-pentafluorophenylbutan-3-one.

^{1}H NMR ($CDCl_3$) δ 2.33 (s, 0.15H), 2.40 (s, 2.85H), 3.42 (s, 4H), 3.94 (d, *J* = 5.6Hz, 0.05H), 4.05 (d, *J* = 7.59Hz, 0.95H), 5.30 (br, 1H).

IR (neat) 3400, 2900, 1730, 1660, 1520, 1140, 990 cm^{-1}

3-Hydroxy-4-methoxy-1-phenyl-1-hexen-5-one.

^{1}H NMR ($CDCl_3$) δ 2.21 (s, 2.46H), 2.24 (s, 0.54H), 2.72 (d, *J* = 5.28Hz, 0.82H), 2.78 (d, *J* = 6.6 Hz, 0.18H), 3.47 (s, 3H), 3.65 (d, *J* = 4.62Hz, 0.18H), 3.72 (d, *J* = 4.94Hz, 0.82H), 4.51-4.57 (m, 1H), 6.18-6.26 (m, 1H), 6.64 (d, *J* = 5.83Hz, 0.82H), 6.67 (d, *J* = 5.84Hz, 0.18H), 7.18-7.42 (m, 5H).

IR (neat) 3400, 3000, 2900, 1720, 1500, 1460, 1360, 1220, 1120, 980, 760, 700 cm^{-1}

3-Hydroxy-4-methoxy-1-phenylhexan-5-one.

^{1}H NMR ($CDCl_3$) δ 1.73-1.81 (m, 2H), 2.19 (s, 3H), 2.40 (br, 1H), 2.67 (dt, *J* = 8.25 and 16.5Hz, 1H), 2.77-2.90 (m, 1H), 3.41 (s, 3H), 3.53 (d, *J* = 4.95Hz, 1H), 3.85 (br, 1H), 7.15-7.30 (m, 5H).

IR (neat) 3450, 3000, 2900, 1720, 1500, 1460, 1360, 1120, 750, 700 cm^{-1}

1-Cyclohexyl-1-hydroxy-2-methoxybutan-3-one.

^{1}H NMR($CDCl_3$) δ 1.03-1.29 (m, 5H), 1.46-1.50 (m, 1H), 1.59-1.87 (m, 5H), 2.22 (s, 0.33H), 2.24 (s, 2.67H), 2.32 (d, *J* = 3.1Hz, 1H), 3.40 (s, 2.67H), 3.44 (s, 0.33H), 3.59-3.67 (m, 2H).

IR (neat) 3450, 2900, 2830, 1720, 1460, 1365, 1230, 1120, 780 cm^{-1}

2,2-Dimethyl-3-hydroxy-4-methoxyhexan-5-one.

^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9H), 1.99 (d, *J* = 6.33Hz, 0.77H), 2.23 (s, 3H), 2.46 (d, *J* = 9.57 Hz, 0.23H), 3.31 (s, 2.31H), 3.42 (s, 0.69H), 3.48-3.68 (m, 2H).

IR (neat) 3430, 2950, 1730, 1490, 1380, 1100 cm^{-1}

1-(3-Chlorobenzoyloxy)-1-methoxypropan-2-one.

^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.62 (s, 3H), 5.97 (s, 1H), 7.43 (t, *J* = 7.92Hz, 1H), 7.57-7.61 (m, 1H), 7.98 (d, *J* = 7.58Hz, 1H), 8.06 (s, 1H).

IR (neat) 3025, 2920, 1750, 1580, 1440, 1370, 1300, 1270, 1210, 1120, 1020, 950, 750 cm^{-1}

The reaction of 1-(3-chlorobenzoyloxy)-1-methoxypropan-2-one with benz-aldehyde to give 1-hydroxy-2-methoxy-1-phenylbutan-3-one.

CH_2Cl_2 (0.5 mL) was added to TiI_4 (125 mg, 0.23 mmol) at ambient temperature under an argon atmosphere. After 10 min stirring, to the solution of TiI_4 was added a solution Ti(O*i*-Pr)$_4$ (1.0 M in CH_2Cl_2, 0.23 mL, 0.23 mmol) at 0˚C. The resulting solution was stirred at ambient temperature for 10 min. A solution of benzaldehyde (15.9 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added to the TiX_4 solution at -78˚C. After 5 min stirring, to the mixture was added a solution of 1-(3-chlorobenzoyloxy)-1-methoxypropan-2-one (74 mg, 0.30 mmol) in CH_2Cl_2 (1.0 mL). After being stirred at -78˚C to -20˚C, the reaction was quenched with sat. aqueous $NaHCO_3$, 5% aqueous $NaHSO_3$, and triethylamine. The mixture was filtered through a Celite pad and extracted with ethyl acetate (10 mLx3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by preparative TLC on silica gel (*n*-hexane : ethyl acetate = 2 : 1 as an eluent) gave 1-hydroxy-2-methoxy-1-phenylbutan-2-one (26.6 mg, 91%).

^{1}H NMR ($CDCl_3$) δ 2.05 (s, 2.82H), 2.07 (s, 0.18H), 3.03 (d, *J* = 4.29Hz, 1H), 3.29 (s, 2.82H), 3.33 (s, 0.18H), 3.76 (d, *J* = 6.27Hz, 1H), 4.88 (dd, *J* = 4.29 and 6.27Hz, 1H), 7.29-7.38 (m, 5H).

IR (neat) 3400, 3000, 2900, 1720, 1460, 1360, 1200, 1120, 700 cm^{-1}