Highly enantioselective Mukaiyama aldol reaction in aqueous conditions using a chiral iron(II) bipyridine catalyst

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Experimental

General

All reactions were performed in flame-dried 12x75 mm culture tubes under an atmosphere of nitrogen or argon. Dimethoxymethane (DME) was distilled from [Na, benzophenone]. Distilled solvents (DME and water) were degassed prior to use (freeze-pump-thaw method). Solid aldehydes were used as received and liquid aldehydes were distilled prior to use. Propiophenone-derived silyl enol ether (Z/E > 99.5:0.5) and 3-pentanone-derived silyl enol ether (Z/E 93:7) were prepared by known procedures using diphenylamide as base and TMSCl as electrophile. Boim’s ligand 1 was synthesized according to known procedures. Iron(II) perchlorate was purchased from Alfa Aesar (reagent grade purity) and iron(II) triflate was synthesized from iron metal (Alfa Aesar®, 99.9+% (metals basis)) and triflic acid. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 400 MHz spectrometer in CDCl₃. For ¹H NMR (400 MHz), tetramethylsilane (TMS) served as internal standard (δ = 0 ppm) and data are reported as follows: chemical shift (in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (in Hz), and integration. For ¹³C NMR (100 MHz), CDCl₃ was used as internal standard (δ = 77.23 ppm) and spectra were obtained with complete proton decoupling. IR spectra were recorded on a BOMEM Arid-Zone™ FT-IR spectrometer or a NICOLET 380 FT-IR spectrometer with ZnSe ATR accessory and are reported in reciprocal centimeter (cm⁻¹). High-resolution mass spectra (HRMS) were recorded on an Agilent 6210 ESI TOF (time of flight) mass spectrometer. Melting points (m.p.) are uncorrected and were recorded on a MEL-TEMP® melting
point apparatus. Flash column chromatography was performed on silica gel (230–400 mesh) and analytical thin-layer chromatography was carried out using 250 µm commercial silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance and/or aqueous potassium permanganate.

Caution: Perchlorate salts can be explosive and should be handled with care. Conversion to lower hydrates by unintentional dehydration may cause explosion. Use due caution in handling, as for all perchlorates.

General Procedure for the Mukaiyama Aldol Reaction of Silyl Enol Ethers with Various Aldehydes

A mixture of Fe(ClO₄)₂·6H₂O (5.4 mg, 0.015 mmol) and Bolm’s ligand 1 (14.8 mg, 0.045 mmol) in degassed DME (0.7 mL) was stirred at room temperature for 1 h. The catalyst solution was then cooled at 0 °C for 10 min and 0.3 mL of degassed water was added. Then the aldehyde (0.30 mmol), benzoic acid (2.2 mg, 0.018 mmol) and the silyl enol ether (0.36 mmol) were subsequently added to the mixture. The reaction mixture was stirred at 0 °C until the aldehyde disappeared completely (monitored by TLC). The reaction was quenched with 5 mL saturated aqueous NaHCO₃. The resulting mixture was extracted with ether (3x10 mL), and the combined organic layers were dried over anhydrous MgSO₄. The solvents were evaporated under reduced pressure (rotary evaporator), and the residue was purified by column chromatography (hexane/ethyl acetate) to give the aldol product. The enantiomeric excess of the product was determined by chiral HPLC analysis.

Characterization data of the aldol products

3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (Table 2, entry 1)

According to the general procedure with 30.5 µL benzaldehyde, the product was isolated as a white solid (m.p. = 44–45 °C). Reaction time = 16 h. Rf (syn) = 0.43; Rf (anti) = 0.39 (20% EtOAc in hexanes). ¹H NMR (CDCl₃, 400 MHz) δ (syn): 7.95 (d, J = 7.2 Hz, 2H), 7.63–7.57 (m, 1H), 7.51–7.46 (m, 2H), 7.44–7.40 (m, 2H), 7.39–7.33 (m, 2H), 7.30–7.25 (m, 1H), 5.26 (dd, J = 2.9, 1.8 Hz, 1H), 3.71 (dq, J = 7.2, 2.9 Hz, 1H), 3.67 (d, J = 1.8 Hz, 1H), 1.20 (d, J = 7.2 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ (syn): 206.0, 142.1, 135.9, 133.9, 129.1, 128.7, 128.5, 127.6, 126.3, 73.4, 47.3, 11.5. IR (neat): 3464, 3061, 3030, 2975, 2934, 2876, 1674, 1596, 1578, 1493, 1449, 1346, 1215, 971, 702 cm⁻¹. [α]D²⁴ +9.3 (c = 1.0, CHCl₃, 97% ee). HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) tR = 28.2 min (minor), tR = 36.6 min (major).
3-Hydroxy-2-methyl-3-(4-methylphenyl)-1-phenylpropan-1-one (Table 2, entry 2)\(^a\)

![Structure](image)

According to the general procedure with 35.5 µL \(p\)-tolualdehyde, the product was isolated as a colorless oil. Reaction time = 16 h. Rf (syn) = 0.48; Rf (anti) = 0.44 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.92 (m, 2H), 7.62–7.57 (m, 1H), 7.51–7.45 (m, 2H), 7.30 (d, \(J = 8.0\) Hz, 2H), 7.17 (d, \(J = 8.0\) Hz, 2H), 5.22 (dd, \(J = 3.1, 2.0\) Hz, 1H), 3.69 (dq, \(J = 7.2, 3.1\) Hz, 1H), 3.57 (d, \(J = 2.0\) Hz, 1H), 2.35 (s, 3H), 1.20 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 206.0, 139.1, 137.2, 135.9, 133.8, 129.2, 129.0, 128.7, 126.2, 73.3, 47.4, 21.4, 11.6. IR (neat): 3466, 3056, 3024, 2976, 2932, 2875, 1674, 1596, 1578, 1514, 1448, 1346, 1215, 971, 817, 706 cm\(^{-1}\). HPLC (Daicel Chiralcel\(^R\) OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) \(t_R = 24.8\) min (minor), \(t_R = 30.2\) min (major).

3-Hydroxy-2-methyl-3-(2-methylphenyl)-1-phenylpropan-1-one (Table 2, entry 3)

![Structure](image)

According to the general procedure with 34.7 µL \(o\)-tolualdehyde, the product was isolated as a white solid (m.p. = 110–111 °C). Reaction time = 24 h. Rf (syn) = 0.43; Rf (anti) = 0.41 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.92 (m, 2H), 7.63–7.58 (m, 2H), 7.52–7.46 (m, 2H), 7.28–7.22 (m, 1H), 7.21–7.12 (m, 2H), 5.43 (dd, \(J = 2.7, 2.1\) Hz, 1H), 3.68 (dq, \(J = 7.2, 2.7\) Hz, 1H), 3.64 (d, \(J = 2.1\) Hz, 1H), 2.32 (s, 3H), 1.24 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 206.3, 139.8, 135.9, 134.0, 133.9, 130.6, 129.1, 128.7, 127.5, 126.9, 69.9, 44.7, 19.5, 11.6. IR (neat): 3474, 3061, 3024, 2976, 2932, 2875, 1674, 1596, 1578, 1514, 1448, 1346, 1215, 971, 817, 706 cm\(^{-1}\). HRMS (ESI-TOF) calcd for \(C_{17}H_{18}O_2Na^+ ([M+Na]^+)\): 277.1199, found: 277.1203. HPLC (Daicel Chiralcel\(^R\) OD-H, hexane/i-PrOH = 99.5/0.5, flow rate = 0.5 mL/min) \(t_R = 24.8\) min (minor), \(t_R = 30.2\) min (major).

3-Hydroxy-3-(4-methoxyphenyl)-2-methyl-1-phenylpropan-1-one (Table 2, entry 4)\(^b\)

![Structure](image)

According to the general procedure with 36.5 µL \(p\)-anisaldehyde, the product was isolated as a white solid (m.p. = 41–43 °C). Reaction time = 16 h. Rf (syn) = 0.31; Rf (anti) = 0.28 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.91 (m, 2H), 7.62–7.56 (m, 1H), 7.51–7.45 (m, 2H), 7.35–7.30 (m, 2H), 6.91–6.86 (m, 2H), 6.11–6.06 (m, 2H), 5.20 (d, \(J = 3.3\) Hz, 1H), 3.81 (s, 3H), 3.68 (dq, \(J = 7.2, 3.3\) Hz, 1H), 3.54 (brs, 1H), 1.21 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 206.0, 159.1, 136.0, 134.3, 133.8, 129.0, 128.7, 127.5, 113.9, 73.1, 55.5, 47.4, 11.7. IR (neat): 3482, 3060, 2966, 2934, 2836, 1674, 1612, 1596, 1513, 1449, 1347, 1303, 1248, 1215, 1176, 1033, 971,
831, 707 cm\(^{-1}\). HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 95/5, flow rate = 0.5 mL/min) \(t_R = 26.9\) min (minor), \(t_R = 33.6\) min (major).

3-(4-Bromophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 5)\(^7\)

![Chemical Structure](image)

According to the general procedure with 55.5 mg 4-bromobenzaldehyde, the product was isolated as a white solid (m.p. = 43–44 °C). Reaction time = 20 h. Rf (syn) = 0.47; Rf (anti) = 0.45 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.92 (m, 2H), 7.64–7.59 (m, 1H), 7.52–7.47 (m, 4H), 7.32–7.27 (m, 2H), 5.22 (dd, \(J = 2.9, 2.0\) Hz, 1H), 3.78 (d, \(J = 2.0\) Hz, 1H), 3.65 (dq, \(J = 7.2, 2.9\) Hz, 1H), 1.17 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 205.8, 141.1, 135.7, 134.0, 131.6, 129.1, 128.7, 128.1, 121.4, 72.7, 47.0, 11.4. IR (neat): 3496, 3082, 2992, 2943, 2865, 1662, 1594, 1577, 1487, 1449, 1396, 1335, 1218, 973, 795, 701 cm\(^{-1}\). HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) \(t_R = 34.1\) min (minor), \(t_R = 41.2\) min (major).

3-(4-Chlorophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 6)\(^8\)

![Chemical Structure](image)

According to the general procedure with 42.2 mg 4-chlorobenzaldehyde, the product was isolated as a white solid (m.p. = 70–71 °C). Reaction time = 24 h. Rf (syn) = 0.39; Rf (anti) = 0.37 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.91 (m, 2H), 7.63–7.58 (m, 1H), 7.51–7.46 (m, 2H), 7.37–7.30 (m, 4H), 5.22 (dd, \(J = 3.1, 2.0\) Hz, 1H), 3.82 (d, \(J = 2.0\) Hz, 1H), 3.66 (dq, \(J = 7.3, 3.1\) Hz, 1H), 1.18 (d, \(J = 7.3\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 205.8, 140.6, 135.7, 134.0, 133.2, 129.1, 128.6, 127.7, 72.7, 47.1, 11.4. IR (neat): 3497, 3066, 2995, 2947, 2866, 1662, 1594, 1578, 1490, 1449, 1399, 1335, 1218, 973, 798, 701 cm\(^{-1}\). HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) \(t_R = 29.4\) min (minor), \(t_R = 36.0\) min (major).

3-(4-Fluorophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 7)\(^9\)

![Chemical Structure](image)

According to the general procedure with 32.2 µL 4-fluorobenzaldehyde, the product was isolated as a white solid (m.p. = 78–79 °C). Reaction time = 20 h. Rf (syn) = 0.39; Rf (anti) = 0.37 (20% EtOAc in hexanes). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) (syn): 7.96–7.92 (m, 2H), 7.63–7.58 (m, 1H), 7.52–7.46 (m, 2H), 7.41–7.35 (m, 2H), 7.08–7.01 (m, 2H), 5.23 (brs, 1H), 3.71 (d, \(J = 2.0\) Hz, 1H), 3.66 (dq, \(J = 7.2, 3.1\) Hz, 1H), 1.19 (d, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) (syn): 205.9, 162.3 (d, \(J = 245.4\) Hz), 137.8 (d, \(J
= 3.1 Hz), 135.8, 134.0, 129.1, 128.7, 127.9 (d, J = 7.7 Hz), 115.3 (d, J = 20.7 Hz), 72.8, 47.2, 11.5. IR (neat): 3480, 3083, 3060, 2993, 2974, 2955, 2933, 2876, 2851, 1663, 1605, 1592, 1509, 1451, 1372, 1220, 972, 833, 712 cm⁻¹. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) tᵣ = 26.5 min (minor), tᵣ = 33.5 min (major).

3-Hydroxy-2-methyl-1-phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (Table 2, entry 8)

According to the general procedure with 41.0 µL 4-(trifluoromethyl)benzaldehyde, the product was isolated as a white solid (m.p. = 38–39 °C). Reaction time = 20 h. Rf (syn) = 0.44; Rf (anti) = 0.40 (20% EtOAc in hexanes). ¹H NMR (CDCl₃, 400 MHz) δ (syn): 7.97–7.94 (m, 2H), 7.66–7.60 (m, 3H), 7.57–7.48 (m, 4H), 5.33 (brs, 1H), 3.91 (d, J = 2.0 Hz, 1H), 3.69 (dq, J = 7.4, 2.7 Hz, 1H), 1.17 (d, J = 7.4 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ (syn): 205.8, 146.0, 135.5, 134.1, 129.8 (q, J = 32.2 Hz), 129.1, 128.8, 126.6, 125.5 (q, J = 3.8 Hz), 124.4 (q, J = 272.3 Hz), 72.7, 46.9, 11.2. IR (neat): 3513, 3069, 3004, 2918, 2895, 1667, 1618, 1598, 1579, 1448, 1415, 1323, 1219, 1157, 1123, 1066, 1018, 973, 856, 808, 699 cm⁻¹. HRMS (ESI-TOF) calcd for C₁₇H₁₅F₃O₂⁺ ([M+Na]⁺): 331.0916, found: 331.0919. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) tᵣ = 28.7 min (minor), tᵣ = 35.5 min (major).

3-Hydroxy-2-methyl-3-(4-nitrophenyl)-1-phenylpropan-1-one (Table 2, entry 9)

According to the general procedure with 45.3 mg 4-nitrobenzaldehyde, the product was isolated as a white solid (m.p. = 111–113 °C). Reaction time = 20 h. Rf (syn) = 0.21; Rf (anti) = 0.18 (20% EtOAc in hexanes). ¹H NMR (CDCl₃, 400 MHz) δ (syn): 8.26–8.22 (m, 2H), 7.98–7.94 (m, 2H), 7.66–7.59 (m, 3H), 7.54–7.48 (m, 2H), 5.37 (dd, J = 2.6, 1.8 Hz, 1H), 4.04 (d, J = 1.8 Hz, 1H), 3.69 (dq, J = 7.3, 2.6 Hz, 1H), 1.16 (d, J = 7.3 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ (syn): 205.5, 149.5, 147.4, 135.3, 134.3, 129.2, 128.8, 127.2, 123.8, 72.5, 46.7, 11.2. IR (neat): 3391, 3110, 3067, 2980, 2942, 2850, 1658, 1598, 1530, 1447, 1340, 1243, 1217, 1102, 975, 870, 708 cm⁻¹. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 90/10, flow rate = 0.5 mL/min) tᵣ = 26.4 min (minor), tᵣ = 31.9 min (major).
3-(4-Cyanophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 10)\textsuperscript{10}

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\begin{array}{c}
\text{O} \\
\text{H} \\
\text{CN}
\end{array}
\]

According to the general procedure with 39.3 mg 4-cyanobenzaldehyde, the product was isolated as a white solid (m.p. = 127–129 °C). Reaction time = 24 h. Rf (\textit{syn}) = 0.19; Rf (\textit{anti}) = 0.17 (20% EtOAc in hexanes). \textit{\textsuperscript{1}}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) (\textit{syn}): 7.97–7.92 (m, 2H), 7.69–7.60 (m, 3H), 7.56–7.47 (m, 4H), 5.31 (d, \(J = 2.6\) Hz, 1H), 3.98 (brs, 1H), 3.67 (dq, \(J = 7.2, 2.6\) Hz, 1H). \textit{\textsuperscript{13}}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) (\textit{syn}): 205.6, 147.4, 135.4, 134.2, 132.4, 129.2, 128.8, 127.1, 119.1, 111.4, 72.6, 46.7, 11.2. IR (neat): 3492, 3061, 2993, 2923, 2864, 2232, 1661, 1608, 1578, 1449, 1403, 1336, 1219, 1183, 862, 799, 700 cm\textsuperscript{–1}. HPLC (Daicel Chiralcel\textsuperscript{®} OD-H, hexane/i-PrOH = 95/5, flow rate = 0.5 mL/min) \(t_R = 46.1\) min (minor), \(t_R = 51.2\) min (major).

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{OH}
\end{array}
\]

3-hydroxy-3-(4-(hydroxymethyl)phenyl)-2-methyl-1-phenylpropan-1-one (Table 2, entry 11)

According to the general procedure with 40.8 mg 4-(hydroxymethyl)benzaldehyde, the product was isolated as a colorless oil. Reaction time = 16 h. Rf (\textit{syn}) = 0.32; Rf (\textit{anti}) = 0.31 (50% EtOAc in hexanes). \textit{\textsuperscript{1}}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) (\textit{syn}): 7.97–7.92 (m, 2H), 7.63–7.57 (m, 1H), 7.52–7.45 (m, 2H), 7.43–7.38 (m, 2H), 7.38–7.33 (m, 2H), 5.25 (brs, 1H), 4.69 (d, \(J = 5.2\) Hz, 2H), 3.70 (dq, \(J = 7.2, 3.1\) Hz, 1H), 3.68 (brs, 1H), 1.73 (t, \(J = 5.2\) Hz, 1H), 1.19 (d, \(J = 7.2\) Hz, 3H). \textit{\textsuperscript{13}}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) (\textit{syn}): 205.9, 141.5, 140.3, 135.9, 133.8, 129.0, 128.7, 127.2, 126.5, 73.4, 65.1, 47.4, 11.7. IR (neat): 3389, 3060, 2975, 2876, 1672, 1596, 1578, 1513, 1448, 1420, 1351, 1215, 1035, 1016, 1001, 973, 821, 795, 707 cm\textsuperscript{–1}. HRMS (ESI-TOF) calcd for C\textsubscript{17}H\textsubscript{18}O\textsubscript{3}Na\textsuperscript{+} ([M+Na\textsuperscript{+}]): 293.1148, found: 293.1145. HPLC (Daicel Chiralcel\textsuperscript{®} OD-H, hexane/i-PrOH = 80/20, flow rate = 0.5 mL/min) \(t_R = 15.7\) min (minor), \(t_R = 22.5\) min (major).

3-Hydroxy-2-methyl-3-(2-naphthyl)-1-phenylpropan-1-one (Table 2, entry 12)\textsuperscript{10}

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\begin{array}{c}
\text{O} \\
\text{H} \\
\end{array}
\]

According to the general procedure with 46.9 mg 2-naphthaldehyde, the product was isolated as a white solid (m.p. = 80–81 °C). Reaction time = 20 h. Rf (\textit{syn}) = 0.41; Rf (\textit{anti}) = 0.38 (20% EtOAc in hexanes). \textit{\textsuperscript{1}}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) (\textit{syn}): 8.00–7.92 (m, 3H), 7.89–7.82 (m, 3H), 7.63–7.58 (m, 1H), 7.52–7.45 (m, 5H), 5.44 (d, \(J = 2.8\) Hz, 1H), 3.87 (brs, 1H), 3.82 (dq, \(J = 7.3, 2.8\) Hz, 1H), 1.21 (d, \(J = 7.3\) Hz, 3H). \textit{\textsuperscript{13}}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) (\textit{syn}): 206.1, 139.4, 135.8, 133.9, 133.5, 133.0, 129.1, 128.8, 128.3, 128.2, 127.9, 126.4, 126.0, 125.2, 124.3, 73.3, 47.1, 11.4. IR (neat): 3485, 3063, 2982, 2938, 2876, 1652, 1597, 1578, 1509, 1448, 1417, 1341, 1216, 1124, 977, 802, 703 cm\textsuperscript{–1}.
HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) $t_R = 62.5 \text{ min (minor)}, t_R = 67.4 \text{ min (major)}$.

3-Hydroxy-2-methyl-3-(1-naphthyl)-1-phenylpropan-1-one (Table 2, entry 13)$^7$

![Chemical Structure](image)

According to the general procedure with 40.7 µL 1-naphthaldehyde, the product was isolated as a colorless oil. Reaction time = 20 h. Rf (syn) = 0.45; Rf (anti) = 0.37 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (syn): 7.99–7.95 (m, 2H), 7.94–7.88 (m, 2H), 7.88–7.85 (m, 1H), 7.64–7.59 (m, 1H), 7.58–7.46 (m, 5H), 6.07 (brs, 1H), 4.14 (d, $J = 2.0$ Hz, 1H), 3.94 (dq, $J = 7.2$, 2.2 Hz, 1H), 1.20 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ (syn): 206.7, 136.9, 135.9, 134.0, 130.0, 129.5, 129.2, 128.8, 128.1, 126.4, 125.7, 125.6, 124.8, 69.5, 45.2, 11.7. IR (neat): 3501, 3058, 2980, 2934, 2876, 1665, 1596, 1578, 1510, 1449, 1353, 1215, 973, 909, 794, 732, 706 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 90/10, flow rate = 0.5 mL/min) $t_R = 18.3 \text{ min (major)}, t_R = 30.2 \text{ min (minor)}$.

(E)-3-Hydroxy-2-methyl-1,5-diphenylpent-4-en-1-one (Table 2, entry 14)$^7$

![Chemical Structure](image)

According to the general procedure with 37.8 µL cinnamaldehyde, the product was isolated as pale yellow oil. Reaction time = 16 h. Rf (syn) = 0.33; Rf (anti) = 0.32 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (syn): 8.01–7.96 (m, 2H), 7.64–7.58 (m, 1H), 7.53–7.47 (m, 2H), 7.41–7.36 (m, 2H), 7.35–7.29 (m, 2H), 7.27–7.22 (m, 1H), 6.73 (d, $J = 15.8$ Hz, 1H), 6.26 (dd, $J = 15.8$, 5.7 Hz, 1H), 4.81 (brs, 1H), 3.65 (dq, $J = 7.2$, 3.1 Hz, 1H), 3.33 (d, $J = 2.0$ Hz, 1H), 1.32 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ (syn): 205.5, 137.0, 136.2, 133.8, 131.3, 129.5, 129.1, 128.8, 128.7, 127.9, 126.8, 72.6, 45.8, 12.2. IR (neat): 3514, 3083, 3059, 3029, 3000, 2948, 2875, 1672, 1597, 1578, 1494, 1449, 1401, 1340, 1216, 1131, 1061, 977, 749, 697 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 90/10, flow rate = 0.5 mL/min) $t_R = 20.6 \text{ min (minor)}, t_R = 36.1 \text{ min (major)}$.

3-Hydroxy-2-methyl-1,5-diphenylpent-4-yn-1-one (Table 2, entry 15)$^7$

![Chemical Structure](image)

According to the general procedure with 36.7 µL phenylpropargyl aldehyde, the product was isolated as a white solid (m.p. = 47–49 °C). Reaction time = 24 h. Rf (syn) = 0.29; Rf (anti) = 0.34 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (syn): 8.02–7.97 (m, 2H), 7.64–7.59 (m, 1H), 7.54–7.48 (m, 2H), 7.42–7.37 (m, 2H), 7.33–7.26 (m, 3H), 7.20–7.00 (m, 3H), 6.57–6.35 (m, 3H), 4.05 (d, $J = 2.0$ Hz, 1H), 3.85 (d, $J = 2.0$ Hz, 1H), 3.62 (d, $J = 2.0$ Hz, 1H), 3.42 (d, $J = 2.0$ Hz, 1H), 3.24 (d, $J = 2.0$ Hz, 1H), 3.05 (d, $J = 2.0$ Hz, 1H), 2.80 (d, $J = 2.0$ Hz, 1H), 2.60 (d, $J = 2.0$ Hz, 1H), 2.40 (d, $J = 2.0$ Hz, 1H), 2.20 (d, $J = 2.0$ Hz, 1H), 2.00 (d, $J = 2.0$ Hz, 1H), 1.80 (d, $J = 2.0$ Hz, 1H), 1.60 (d, $J = 2.0$ Hz, 1H), 1.40 (d, $J = 2.0$ Hz, 1H), 1.20 (d, $J = 2.0$ Hz, 1H).
5.09 (d, $J = 3.9$ Hz, 1H), 3.80 (dq, $J = 7.2, 3.9$ Hz, 1H), 3.28 (brs, 1H), 1.51 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ (syn): 204.3, 135.9, 133.9, 132.0, 129.1, 128.8, 128.7, 128.5, 122.6, 88.1, 85.7, 64.0, 46.5, 13.0. IR (neat): 3295, 3062, 2974, 2935, 2876, 2238, 1677, 1596, 1489, 1448, 1346, 1206, 1027, 978, 761, 707, 690 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 90/10, flow rate = 0.5 mL/min) $t_R = 19.7$ min (minor), $t_R = 43.5$ min (major).

**3-Hydroxy-2-methyl-1-phenyldene-4-yn-1-one (Table 2, entry 16)**

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \]

According to the general procedure with 42.8 µL 2-octynal, the product was isolated as a colorless oil. Reaction time = 24 h. RF (syn) = 0.39; RF (anti) = 0.43 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (syn): 7.98–7.93 (m, 2H), 7.62–7.57 (m, 1H), 7.52–7.46 (m, 2H), 7.35 (brs, 1H), 6.35–6.30 (m, 2H), 5.23 (d, $J = 4.0$ Hz, 1H), 3.94 (dq, $J = 7.2$, 4.0 Hz, 1H), 3.31 (brs, 1H), 1.30 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ (syn): 204.9, 154.8, 141.9, 135.8, 133.8, 129.0, 128.8, 110.6, 107.0, 68.9, 44.9, 12.7. IR (neat): 3447, 3116, 3062, 2974, 2917, 2877, 2849, 1677, 1596, 1579, 1504, 1449, 1372, 1216, 1148, 1001, 972, 740, 710 cm$^{-1}$. HRMS (ESI-TOF) calcd for C$_{17}$H$_{22}$O$_2$Na$^+$ ([M+Na]$^+$): 281.1512, found: 281.1516. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 90/10, flow rate = 0.5 mL/min) $t_R = 11.6$ min (minor), $t_R = 16.0$ min (major).

**3-(2-Furyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 17)**

\[ \begin{array}{c}
\text{O} \\
\text{O} \\
\text{H} \\
\end{array} \]

According to the general procedure with 24.8 µL furfural, the product was isolated as a colorless oil. Reaction time = 16 h. RF (syn) = 0.31; RF (anti) = 0.30 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ (syn): 8.00–7.94 (m, 2H), 7.63–7.57 (m, 1H), 7.52–7.46 (m, 2H), 7.35 (brs, 1H), 6.35–6.30 (m, 2H), 5.23 (d, $J = 4.0$ Hz, 1H), 3.94 (dq, $J = 7.2$, 4.0 Hz, 1H), 3.31 (brs, 1H), 1.30 (d, $J = 7.2$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ (syn): 204.9, 154.8, 141.9, 135.8, 133.8, 129.0, 128.8, 110.6, 107.0, 68.9, 44.9, 12.7. IR (neat): 3447, 3116, 3062, 2974, 2917, 2877, 2849, 1677, 1596, 1579, 1504, 1449, 1372, 1216, 1148, 1001, 972, 740, 710 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) $t_R = 34.5$ min (minor), $t_R = 41.8$ min (major).
3-Hydroxy-2-methyl-1-phenyl-3-(thiophen-2-yl)propan-1-one (Table 2, entry 18)

According to the general procedure with 28.0 µL 2-thiophenecarboxaldehyde, the product was isolated as a white solid (m.p. = 45–46 °C). Reaction time = 24 h. Rf (syn) = 0.39; Rf (anti) = 0.38 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) δ (syn): 7.97–7.93 (m, 2H), 7.63–7.58 (m, 1H), 7.52–7.46 (m, 2H), 7.24 (dd, $J$ = 4.9, 1.4 Hz, 1H), 7.02–6.96 (m, 2H), 5.49 (dd, $J$ = 3.7, 0.8 Hz, 1H), 3.80 (dq, $J$ = 7.2, 3.7 Hz, 1H), 3.60 (brs, 1H), 1.33 (d, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz) δ (syn): 205.2, 146.1, 135.8, 133.9, 129.1, 128.7, 126.9, 124.5, 123.8, 70.7, 47.9, 12.5. IR (neat): 3458, 3117, 3071, 2985, 2933, 1668, 1593, 1576, 1449, 1376, 1354, 1199, 1180, 1035, 1020, 972, 838, 706 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) $t_R = 36.9$ min (minor), $t_R = 45.8$ min (major).

3-Cyclohexyl-3-hydroxy-2-methyl-1-phenylpropan-1-one (Table 2, entry 19)

According to the general procedure with 36.1 µL cyclohexanecarboxaldehyde, the product was isolated as a colorless oil. Reaction time = 16 h. Rf (syn) = 0.46; Rf (anti) = 0.53 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) δ (syn): 7.97–7.91 (m, 2H), 7.62–7.56 (m, 1H), 7.52–7.46 (m, 2H), 3.72–3.65 (m, 2H), 3.09 (d, $J$ = 2.3 Hz, 1H), 2.12 (d, $J$ = 13.1 Hz, 1H), 1.83–0.92 (m, 10H), 1.24 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (syn): 206.2, 136.1, 133.6, 129.0, 128.7, 75.7, 41.5, 40.4, 29.7, 29.4, 26.6, 26.4, 26.1, 10.8. IR (neat): 3497, 3062, 2925, 2852, 1677, 1596, 1579, 1448, 1345, 1313, 1264, 1216, 1079, 971, 709 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) $t_R = 14.7$ min (minor), $t_R = 17.7$ min (major).

3-Hydroxy-2,4,4-trimethyl-1-phenylpentan-1-one (Table 2, entry 20)

According to the general procedure with 33.3 µL trimethylacetaldehyde, the product was isolated as a white solid (m.p. = 74–75 °C). Reaction time = 24 h. Rf (syn) = 0.50; Rf (anti) = 0.58 (20% EtOAc in hexanes). $^1$H NMR (CDCl$_3$, 400 MHz) δ (syn): 7.99–7.94 (m, 2H), 7.62–7.56 (m, 1H), 7.52–7.46 (m, 2H), 3.81–3.74 (m, 2H), 2.64 (brs, 1H), 1.28 (d, $J$ = 6.8 Hz, 3H), 0.99 (s, 9H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ (syn): 205.6, 135.9, 133.6, 129.0, 128.7, 77.8, 41.2, 35.9, 27.2, 13.4. IR (neat): 3529, 3062, 2970, 2873, 1674, 1596, 1579, 1448, 1365, 1301, 1206, 1064, 967, 710 cm$^{-1}$. HPLC (Daicel Chiralcel® OD-H, hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min) $t_R = 18.8$ min (minor), $t_R = 23.8$ min (major).
3-Hydroxy-2-methyl-1-phenylhexan-1-one (Table 2, entry 21)\textsuperscript{13}

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{OH}
\end{array}
\]

According to the general procedure with 27.0 \(\mu\)L butyraldehyde, the product was isolated as a colorless oil. Reaction time = 16 h. \(\text{Rf} (\text{syn}) = 0.40; \text{Rf} (\text{anti}) = 0.44 \) (20\% EtOAc in hexanes). \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta (\text{syn}): 7.99–7.93 \) (m, 2H), 7.63–7.57 (m, 1H), 7.53–7.47 (m, 2H), 4.10–4.02 (m, 1H), 3.48 (dq, \(J = 7.2, 2.9 \) Hz, 1H), 3.09 (brs, 1H), 1.68–1.48 (m, 2H), 1.48–1.34 (m, 2H), 1.27 (d, \(J = 7.2 \) Hz, 3H), 0.96 (t, \(J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta (\text{syn}): 206.2, 136.2, 133.7, 129.0, 128.7, 71.3, 44.8, 36.7, 19.5, 14.3, 11.3. IR (neat): 3447, 3064, 2960, 2934, 2873, 1676, 1596, 1579, 1449, 1369, 1308, 1255, 1214, 1120, 1075, 972, 708 cm\textsuperscript{–1}. HPLC (Daicel Chiralcel\textsuperscript{®} OD-H, hexane/i-PrOH = 99.5/0.5, flow rate = 0.5 mL/min) \(t_R = 35.1 \) min (minor), \(t_R = 45.9 \) min (major).

1-Hydroxy-2-methyl-1-phenylpentan-3-one (Table 3, entry 1)\textsuperscript{14}

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{OH}
\end{array}
\]

According to the general procedure with 30.5 \(\mu\)L benzaldehyde, the product was isolated as a colorless oil. Reaction time = 16 h. \(\text{Rf} (\text{syn}) = 0.38; \text{Rf} (\text{anti}) = 0.37 \) (20\% EtOAc in hexanes). \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta (\text{syn}): 7.37–7.24 \) (m, 5H), 5.07 (d, \(J = 4.0 \) Hz, 1H), 3.13 (s, 1H), 2.85 (dq, \(J = 7.2, 4.0 \) Hz, 1H), 2.52 (qd, \(J = 7.2, 18.1 \) Hz, 1H), 2.35 (qd, \(J = 7.2, 18.1 \) Hz, 1H), 1.09 (d, \(J = 7.2 \) Hz, 3H), 1.01 (t, \(J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta (\text{syn}): 216.6, 142.0, 128.5, 127.6, 126.2, 73.5, 52.5, 35.7, 10.8, 7.7. IR (neat): 3460, 3063, 3031, 2977, 2938, 2873, 1676, 1705, 1604, 1494, 1454, 1408, 1378, 1357, 1197, 1117, 1015, 975, 762, 702 cm\textsuperscript{–1}. HPLC (Daicel Chiralcel\textsuperscript{®} OJ-H, hexane/i-PrOH = 95/5, flow rate = 0.5 mL/min) \(t_R = 27.0 \) min (minor), \(t_R = 29.8 \) min (major).

5-Hydroxy-4-methyl-7-phenylheptan-3-one (Table 3, entry 2)\textsuperscript{11}

\[
\begin{array}{c}
\text{O} \\
\text{C} \\
\text{OH}
\end{array}
\]

According to the general procedure with 39.6 \(\mu\)L 3-phenylpropionaldehyde, the product was isolated as a colorless oil. Reaction time = 16 h. \(\text{Rf} (\text{syn}) = 0.31; \text{Rf} (\text{anti}) = 0.31 \) (20\% EtOAc in hexanes). \(^1\)H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta (\text{syn}): 7.32–7.25 \) (m, 2H), 7.24–7.17 (m, 3H), 3.97–3.90 (m, 1H), 2.9 (brs, 1H), 2.90–2.80 (m, 1H), 2.71–2.38 (m, 4H), 1.90–1.78 (m, 1H), 1.65–1.54 (m, 1H), 1.15 (d, \(J = 7.2 \) Hz, 3H), 1.05 (t, \(J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta (\text{syn}): 217.1, 142.1, 128.7, 128.6, 126.1, 70.5, 50.0, 36.0, 35.3, 32.6, 10.3, 7.8. IR (neat): 3452, 3063, 2977, 2938, 2879, 1705, 1604, 1494, 1454, 1408, 1378, 1357, 1197, 1117, 1015, 975, 762, 702 cm\textsuperscript{–1}. HPLC (Daicel Chiralpak\textsuperscript{®} AD-H, hexane/i-PrOH = 98/2, flow rate = 0.5 mL/min) \(t_R = 30.7 \) min (minor), \(t_R = 32.2 \) min (major).
Crystallization of \([\text{Fe(ClO}_4\text{)}_2\cdot 1\cdot \text{(H}_2\text{O)}\cdot \text{DME complexe}}\]

Crystallization of \([\text{Fe(ClO}_4\text{)}_2\cdot 1\cdot \text{(H}_2\text{O)}\cdot \text{DME complexe}}\] was carried out as follows: A mixture of \(\text{Fe(ClO}_4\text{)}_2\cdot 6\text{H}_2\text{O}\) (5.6 mg, 15.4 µmol) and Bolm’s ligand 1 (5.1 mg, 15.4 µmol) was dissolved in DME (0.2 mL). This solution was stirred at room temperature for 30 min. Vapor diffusion of diethyl ether into this solution afforded the crystals. CCDC 828098 \((1\cdot \text{Fe}\cdot \text{DME}\cdot \text{H}_2\text{O})^{2+}\cdot 2\text{ClO}_4^-\) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.au.uk/data_request/cif.

References


[3] Iron powder (111.7 mg, 2 mmol) was suspended in 2 mL distilled water and freshly distilled triflic acid (354 µL, 4 mmol) was added. The mixture was refluxed for 30 minutes and the resulting solution was filtered and evaporated. The white solid obtained was dried under high vacuum to afford \(\text{Fe(OTf)}_2\cdot \text{H}_2\text{O}\) quantitatively. Thermogravimetric analysis confirmed the presence of one hydration water molecule.


[6] A control experiment with propiophenone-derived silyl enol ether and benzaldehyde using non degassed solvents afforded the product with the same yield and selectivities as the same reaction using oxygen-free solvents. This result adds further evidence that Fe(III) catalysis is not involved in our reaction conditions.


syn (major) + anti (minor)
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syn (major) + anti (minor)
syn (major) + anti (minor)