Lewis Base-catalyzed Conjugate Reduction and Reductive Aldol Reaction of α,β-Unsaturated Ketones Using Trichlorosilane

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General Methods

Melting points (Mp) are uncorrected. 1H and 13C NMR spectra were measured in CDCl3 with JEOL JNM-ECX400 spectrometer. Tetramethylsilane (TMS) (δ = 0 ppm) and CDCl3 (δ = 77.0 ppm) served as internal standards for 1H and 13C NMR, respectively. Infrared spectra were recorded on JASCO IR Report-100. Mass spectra were measured with JEOL JMS-DX303HF mass spectrometer. Optical rotations were recorded on JASCO P-1010 polarimeter. High-pressure liquid chromatography (HPLC) was performed on JASCO P-980 and UV-1575.

Thin-layer chromatography (TLC) analysis was carried out using Merck silica gel plates. Visualization was accomplished with UV light, phosphomolybdic acid and/or anisaldehyde. Column chromatography was performed using Kanto Chemical Silica Gel 60N (spherical, neutral, 63-210 μm).
All reactions were performed under argon atmosphere using oven- and heating gun-dried glassware equipped with a rubber septum and a magnetic stirring bar.

**Solvents and Chemicals**

Dry dichloromethane (dehydrated) was purchased from Kanto Chemical and stored over 4Å MS prior to use. All other solvents were purified based on standard procedures.

Trichlorosilane was purchased from Tokyo Kasei Kogyo (TCI) and used without further purification. (S)-BINAP dioxide (BINAPO) was prepared by oxidation of (S)-BINAP with hydrogen peroxide in acetone. All other chemicals were purified based on standard procedures.

Starting materials: (E)-4-Phenyl-3-buten-2-one (benzalacetone, 1a), (E)-1,3-diphenyl-2-propen-1-one (chalcone, 1b), α- and β-ionone (1e and 1f) and (R)-(+)–pulegone (1k) were obtained commercially and used after purification by standard procedures. (E)-1-Phenyl-2-buten-1-one (1c) was prepared by oxidation of (E)-1-phenyl-2-buten-1-ol with MnO₂. Dibenzylideneacetone (1d), 2-benzylidene cyclohexanone (1i) and 2,6-dibenzylidene cyclohexanone (1j) were prepared by aldol condensation. 2-Methyl-1-phenyl-2-propen-1-one (1h) was prepared by Mannich reaction of propiophenone with hexamethylenetetramine and acetic anhydride. (E)-1,3-Diphenyl-2-methyl-2-propen-1-one (1g) was prepared according to the literatures.

**General Procedure for Conjugate Reduction**

To a solution of a Lewis base [HMPA, Ph₃P=O (20 mol%) or (S)-BINAPO (10 mol%)] and an enone (1.0 or 0.5 mmol) in dry dichloromethane (2 or 1 mL) was added dropwise trichlorosilane (1.5–3 M CH₂Cl₂ solution, 2 equiv) at 0 °C. The reaction was monitored by TLC analysis. For the reactions of less reactive enones, the temperature was raised to ambient temperature. After the starting material was consumed or no significant change was observed, the reaction was quenched with sat. aqueous NaHCO₃ (3 mL). After addition of ethyl acetate (10 mL), the mixture was stirred for 1 h, filtered through a Celite pad with ethyl acetate and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (1×), dried over anhydrous MgSO₄, filtered, evaporated and purified by silica gel column chromatography (hexane/ethyl acetate = 20/1~8/1) to give a reduction product.
4-Phenylbutan-2-one (2a) (Table 1, entry 1)

According to the general procedure, the reaction of benzalacetone (1a) (145.6 mg) with HMPA and HSiCl3 (0 °C, 30 min) gave the reduction product (127.7 mg, 87% yield). The product was identified in comparison with a commercially available sample.

1,3-Diphenylpropan-1-one (Table 1, entry 2)

According to the general procedure, the reaction of chalcone (1b) (208.3 mg) with HMPA and HSiCl3 (0 °C, 30 min) gave the reduction product (191.7 mg, 91% yield). The product was identified in comparison with a commercially available sample.

1-Phenylbutan-1-one (butyrophenone) (Table 1, entry 3)

According to the general procedure, the reaction of (E)-1-phenyl-2-buten-1-one (1c) (74.8 mg) with HMPA and HSiCl3 (0 °C, 30 min) gave the reduction product (54.3 mg, 72% yield). The product was identified in comparison with a commercially available sample.

(E)-1,5-Diphenyl-1-penten-3-one (Table 1, entry 4)

According to the general procedure, the reaction of dibenzylideneacetone (1d) (111.7 mg) with HMPA and HSiCl3 (0 °C, 60 min) gave the reduction product (89.7 mg, 80% yield). Spectroscopic data were consistent with the literature data.4

4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)butan-2-one (Table 1, entry 5)

According to the general procedure, the reaction of α-ionone (1e) (192.2 mg) with HMPA and HSiCl3 (0 °C, 4 h then rt, 2 h) gave the reduction product (180.7 mg, 93% yield). Spectroscopic data were consistent with the literature data.4

4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)butan-2-one (Table 1, entry 6)

According to the general procedure, the reaction of β-ionone (1f) (192.3 mg) with HMPA and HSiCl3 (0 °C, 30 min) gave the reduction product (182.2 mg, 94% yield). Spectroscopic data were consistent with the literature data.4
(±)-1,3-Diphenylbutan-1-one (Table 1, entry 7)

According to the general procedure, the reaction of 1,3-diphenyl-2-methyl-2-propen-1-one (1g) (112.0 mg) with HMPA and HSiCl₃ (0 °C, 5 h then rt, 19 h) gave the reduction product (83.4 mg, 74% yield). Spectroscopic data were consistent with the literature data.⁵

2-Methyl-1-Phenylpropan-1-one (isobutyrophenone) (Table 1, entry 8)

According to the general procedure, the reaction of 2-methyl-1-phenyl-2-propen-1-one (1h) (65.8 mg) with HMPA and HSiCl₃ (0 °C, 9 h then rt, 17 h) gave the reduction product (39.7 mg, 60% yield). The product was identified in comparison with a commercially available sample.

2-Benzylcyclohexanone (Table 1, entry 9)

According to the general procedure, the reaction of 2-benzylidenecyclohexanone (1i) (92.6 mg) with HMPA and HSiCl₃ (0 °C, 30 min) gave the reduction product (83.5 mg, 89% yield). The product was identified in comparison with a commercially available sample.

2-Benzylidene-6-benzylcyclohexanone (Table 1, entry 10)

According to the general procedure, the reaction of 2,6-dibenzylidenecyclohexanone (1j) (137.5 mg) with HMPA and HSiCl₃ (0 °C, 40 min) gave the reduction product (114.0 mg, 82% yield). Slightly yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 1.50-1.65 (m, 2H), 1.83-2.00 (m, 2H), 2.58-2.73 (m, 3H), 2.94-3.04 (m, 1H), 3.40 (apparent q, J = 8.9 Hz, 1H), 7.18-7.24 (m, 3H), 7.26-7.36 (m, 3H), 7.36-7.42 (m, 4H), 7.46 (t, J = 2.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.8, 28.4, 29.2, 36.9, 51.2, 126.2, 128.49, 128.58, 129.4, 130.3, 135.4, 135.9, 137.5, 140.3, 203.4; HRMS (FAB): calcd for C₂₀H₂₁O (M+H⁺) 277.1592, found 277.1590; Elemental Analysis calcd (%) for C₂₀H₂₀O: C 86.92, H 7.29; found: C 86.73, H 7.41.

(5R)-2-Isopropyl-5-methylcyclohexanone (Table 1, entry 11)

According to the general procedure, the reaction of (R)-(+)–pulegone (1k) (151.7 mg) with HMPA and HSiCl₃ (0 °C, 4 h then rt, 16 h) gave the reduction
product (128.6 mg, 84% yield) as a diastereomeric mixture ($trans/cis = 1.7/1$). Spectroscopic data were consistent with a commercially available sample [(-)-menthone] and the literature data.4

**((S)-1,3-Diphenylbutan-1-one (Scheme 2)**

According to the general procedure, the reaction of 2-methyl-1-phenyl-2-propen-1-one (1g) (111.8 mg) with (S)-BINAPO and HSiCl$_3$ (0 °C, 20 h) gave the reduction product (109.7 mg, 97% yield) with 97% ee (S). Spectroscopic data were consistent with the reported data and the absolute configuration was assigned in comparison of the optical rotation with the literature value.5 Colourless liquid; $[\alpha]_{23}^{23}$D $+14.7$ (c 1.005, CCl$_4$) for 97% ee (S) [lit. 5 $[\alpha]_{25}^{25}$D $-13.5$ (c 1.00, CCl$_4$) for 82% ee (R)]; HPLC (a combination of CHIRALPAK AD-H and AS-H, 0.46 cm $\times$ 25 cmL each, hexane/2-propanol = 39/1, flow rate 1.0 mL/min, UV detection at 254 nm) $t_R = 14.4$ min (S), 15.8 min (R).

**1H NMR Analysis of Reduction of Benzalacetone with Trichlorosilane**

To a solution of benzalacetone (27.5 mg) and Ph$_3$P=O (10.5 mg) in CD$_2$Cl$_2$ (0.6 mL) in a NMR tube capped with a rubber septum was added trichlorosilane (38 μL). Gradual formation of the corresponding (Z)-trichlorosilyl enolate was observed by $^1$H NMR analysis. After 4 h, almost the starting material (>95%) was consumed. The geometry of the enolate was assigned based on a NOESY analysis of the reaction mixture (Chart 1).

**(Z)-2-(Trichlorosilyloxy)-4-phenyl-2-butene**

$^1$H NMR (400 MHz, CD$_2$Cl$_2$, internal standard: solvent residual peak = 5.32 ppm) $\delta$ 2.35 (s, 3H), 3.41 (d, $J = 7.3$ Hz, 2H), 4.95 (t, $J = 7.3$ Hz, 1H), 7.15-7.24 (m, 3H), 7.24-7.33 (m, 2H).
**Chart 1.** The NOESY spectrum of the trichlorosilyl enolate derived from benzalacetone.

**General Procedure for Reductive Aldol Reaction**

To a solution of a Lewis base [HMPA, Ph₃P=O (20 mol%) or (S)-BINAP (10 mol%)], an enone (0.5 mmol) and an aldehyde (0.6 mmol, 1.2 equiv) in dry dichloromethane (2 mL) was added dropwise trichlorosilane (ca. 3 M CH₂Cl₂ solution, 2 equiv) at the indicated temperature. The reaction was monitored by TLC analysis. After the enone was consumed or no significant change was observed, the reaction was quenched with sat. aqueous NaHCO₃ (3 mL). After addition of ethyl acetate (10 mL), the mixture was stirred for 1 h, filtered through a Celite pad with ethyl acetate and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (1×), dried over anhydrous MgSO₄, filtered, evaporated and purified by silica gel column chromatography (hexane/ethyl acetate = 20/1~3/1) to give the corresponding aldol product.
2-Benzyl-1,3-diphenyl-3-hydroxypropan-1-one (Table 2, entry 2)

According to the general procedure, the reaction of chalcone (1b) (104.2 mg) and benzaldehyde (61 μL) with Ph3P=O and HSiCl3 (0 °C, 4 h) gave the aldol product (123.3 mg, 78% yield) as a diastereomeric mixture (50:50). Spectroscopic data were consistent with the literature data.6,7

2-Benzyl-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (Table 2, entry 3)

According to the general procedure, the reaction of chalcone (1b) (104.2 mg) and p-anisaldehyde (73 μL) with Ph3P=O and HSiCl3 (0 °C, 4 h) gave the aldol product (120.0 mg, 69% yield) as a diastereomeric mixture (52:48). Colourless viscous oil; IR (film on NaCl, cm–1) 3450, 1670, 1610, 1593, 1578, 1511, 1247, 1175, 1035, 700; 1H NMR (400 MHz, CDCl3) δ 2.79 (dd, J = 13.3, 5.5 Hz, 0.48H), 2.99 (dd, J = 13.3, 8.9 Hz, 0.48H), 3.10 (dd, J = 13.6, 3.7 Hz, 0.52H), 3.17 (dd, J = 13.6, 10.1 Hz, 0.52H), 3.30 (brs, 0.52H), 3.36 (brs, 0.48H), 3.72 (s, 1.56H), 3.73 (s, 1.44H), 3.98-4.10 (m, 1H), 4.91 (brd, J = 6.4 Hz, 0.48H), 5.02 (d, J = 5.0 Hz, 0.52H), 6.80 (d, J = 9.4 Hz, 1.04H), 6.82 (d, J = 9.4 Hz, 0.96H), 6.95-7.43 (m, 10H), 7.49 (d, J = 7.3 Hz, 1.04H), 7.66 (d, J = 7.3 Hz, 0.96H); 13C NMR (100 MHz, CDCl3) δ 33.9, 36.5, 55.0, 55.1, 55.8, 73.7, 75.3, 113.6, 113.8, 126.00, 126.24, 127.35, 127.40, 128.06, 128.14, 128.19, 128.24, 128.30, 128.86, 128.92, 132.84, 132.89, 133.72, 134.67, 137.37, 138.08, 138.57, 139.26, 158.82, 159.00, 204.6, 205.5; HRMS (FAB): calcd for C23H22O3Na (M+Na+) 369.1467, found 369.1474.

2-Benzyl-3-hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (Table 2, entry 4)

According to the general procedure, the reaction of chalcone (1b) (104.6 mg) and p-nitrobenzaldehyde (90.9 mg) with Ph3P=O and HSiCl3 (0 °C, 4 h) gave the aldol product (130.7 mg, 72% yield) as a diastereomeric mixture (74:26). Colourless solid; Mp = 122-126 °C; IR (film on NaCl, cm–1) 3460, 1670, 1592, 1516, 1343, 698; 1H NMR (400 MHz, CDCl3) δ 2.96 (dd, J = 13.3, 4.1 Hz, 0.26H), 3.04 (dd, J = 13.5, 7.8 Hz, 0.74H), 3.11 (dd, J = 13.5, 7.3 Hz, 0.74H), 3.17 (dd, J = 13.8, 10.3 Hz, 0.26H), 3.86 (d, J = 1.8 Hz, 0.26H), 4.00-4.12 (m, 1H), 4.38 (d, J = 8.2 Hz, 0.74H), 4.99 (dd, J = 8.2, 4.6 Hz, 0.74H), 5.20 (brd, J = 1.8 Hz, 0.26H), 6.92 (d, J = 7.1 Hz, 0.52H), 6.99-7.10 (m, 0.78H), 7.14-7.36 (m, 5.70H), 7.41-7.50 (m, 2.48H), 7.54-7.61 (m, 1.04H), 7.66 (d, J = 7.6 Hz, 1.48H), 8.07 (d, J = 8.7 Hz, 1.48H), 8.14 (d, J = 8.7 Hz, 0.52H); 13C NMR (100 MHz, CDCl3) δ 33.9, 36.5, 55.0, 55.1, 55.8, 73.7, 75.3, 113.6, 113.8, 126.00, 126.24, 127.35, 127.40, 128.06, 128.14, 128.19, 128.24, 128.30, 128.86, 128.92, 132.84, 132.89, 133.72, 134.67, 137.37, 138.08, 138.57, 139.26, 158.82, 159.00, 204.6, 205.5; HRMS (FAB): calcd for C23H22O3N (M+H+) 353.1212, found 353.1213.
MHz, CDCl\textsubscript{3}) \(\delta\) 33.4, 36.4, 53.6, 54.6, 72.9, 73.6, 123.5, 126.3, 126.67, 126.76, 127.09, 128.05, 128.21, 128.32, 128.43, 128.58, 128.64, 128.83, 128.95, 133.51, 133.75, 136.62, 136.72, 137.8, 138.3, 147.03, 147.10, 149.0, 150.3, 204.4, 205.0; HRMS (FAB): calcd for C\textsubscript{22}H\textsubscript{20}O\textsubscript{4} (M+H\textsuperscript{+}) 362.1392, found 362.1385.

2-Benzyl-1,5-diphenyl-3-hydroxypentan-1-one (Table 2, entry 5)

According to the general procedure, the reaction of chalcone (1b) (104.1 mg) and hydrocinnamaldehyde (79 \(\mu\)L) with Ph\textsubscript{3}P=O and HSiCl\textsubscript{3} (rt, 24 h) gave the aldol product (33.1 mg, 19% yield) as a diastereomeric mixture (52:48). Colourless viscous oil; IR (film on NaCl, cm\textsuperscript{-1}) 3450, 1667, 1590, 1575, 1490, 1445, 693; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) less polar isomer (major): \(\delta\) 1.63-1.82 (m, 2H), 2.54-2.63 (m, 1H), 2.79-2.90 (m, 1H), 3.07 (dd, \(J = 13.8, 6.9\) Hz, 1H), 3.11 (dd, \(J = 13.8, 7.8\) Hz, 1H), 3.41 (d, \(J = 9.2\) Hz, 1H), 3.70-3.84 (m, 2H), 7.05-7.26 (m, 10H), 7.40 (apparent t, \(J = 7.8\) Hz, 2H), 7.54 (apparent t, \(J = 7.3\) Hz, 1H), 7.79 (apparent d, \(J = 8.0\) Hz, 2H); polar isomer (minor): \(\delta\) 1.76-1.88 (m, 1H), 1.90-2.03 (m, 1H), 2.64-2.74 (m, 1H), 2.76-2.92 (m, 2H), 3.10 (dd, \(J = 13.7, 5.0\) Hz, 1H), 3.15 (dd, \(J = 13.7, 9.2\) Hz, 1H), 3.78 (ddd, \(J = 9.2, 5.0, 3.7\) Hz, 1H), 3.94-4.00 (m, 1H), 7.05-7.21 (m, 8H), 7.24-7.33 (m, 4H), 7.46 (apparent t, \(J = 7.3\) Hz, 1H), 7.62 (apparent d, \(J = 7.4\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}) less polar isomer: \(\delta\) 32.6, 36.5, 38.2, 52.0, 71.9, 125.8, 126.5, 128.23, 128.33, 128.39, 128.52, 128.70, 129.1, 133.6, 137.3, 138.7, 141.8, 206.4; polar isomer: \(\delta\) 32.4, 33.6, 36.5, 53.2, 71.5, 126.0, 126.2, 128.3, 128.4, 129.0, 133.2, 137.2, 139.4, 141.6, 205.1; HRMS (FAB): calcd for C\textsubscript{24}H\textsubscript{25}O\textsubscript{2} (M+H\textsuperscript{+}) 345.1855, found 345.1865.

2-Ethyl-1,3-diphenyl-3-hydroxypropan-1-one (Table 2, entry 6)

According to the general procedure, the reaction of (E)-1-phenyl-2-buten-1-one (1c) (73.4 mg) and benzaldehyde (61 \(\mu\)L) with Ph\textsubscript{3}P=O and HSiCl\textsubscript{3} (0 °C, 4 h) gave the aldol product (88.8 mg, 70% yield) as a diastereomeric mixture (39:61). Spectroscopic data were consistent with the literature data.\(^7\)

4-Hydroxy-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl-4-phenylbutan-2-one (Table 2, entry 7)

According to the general procedure, the reaction of \(\beta\)-ionone (1f) (81.4 mg) and benzaldehyde (61 \(\mu\)L) with Ph\textsubscript{3}P=O and HSiCl\textsubscript{3} (0 °C, 5 h)
gave the aldol product (82.6 mg, 65% yield) as a diastereomeric mixture (78:22). Spectroscopic data were consistent with the literature data.\(^7\)

**2,2-Dimethyl-1,3-diphenyl-3-hydroxypropan-1-one (Table 2, entry 8)**

According to the general procedure, the reaction of 2-methyl-1-phenylpropenone (1h) (73.5 mg) and benzaldehyde (61 µL) with HMPA and HSiCl\(_3\) (rt, 24 h) gave the aldol product (50.2 mg, 39% yield). Spectroscopic data were consistent with the literature data.\(^8\)

*(3R,4R)-4-Hydroxy-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl-4-phenylbutan-2-one (Scheme 2)*

According to the general procedure, the reaction of \(\beta\)-ionone (1f) (96.5 mg) and benzaldehyde (120 µL, 2 equiv) with (S)-BINAP and HSiCl\(_3\) (–78 °C, 21 h) gave the syn-aldol product (101.0 mg, 67% yield, 96% ee) and the anti-aldol product including impurities (5.3 mg, 0% ee). The diastereomers were separable by column chromatography. The diastereoselectivity was determined by \(^1\)H NMR analysis of the crude reaction mixture. Spectroscopic data were consistent with the reported data\(^6\) and the absolute configuration was assigned in comparison of the optical rotation with the literature value.\(^6\)

*Syn*-isomer: Colourless solid; \([\alpha]^{20}_D +56.9\) (c 1.01, CHCl\(_3\)) for 58% ee (3R,4R) \([\text{lit}^6 [\alpha]^{20}_D - 57.7\) (c 1.0, CHCl\(_3\)) for 75% ee (3S,4S)]; HPLC (a combination of two CHIRALPAK AD-H, 0.46 cmø × 25 cmL each, hexane/2-propanol = 29/1, flow rate 1.0 mL/min, UV detection at 254 nm) \(t_R = 17.8\) min (3S,4S), 21.3 min (3R,4R).

*Anti*-isomer: HPLC (a combination of two CHIRALPAK AD-H, 0.46 cmø × 25 cmL each, hexane/2-propanol = 29/1, flow rate 1.0 mL/min, UV detection at 254 nm) \(t_R = 18.4\) min, 20.0 min.
$^1$H and $^{13}$C NMR Spectra of All New Compounds
HPLC Traces of the Optically Active Products

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