Electronic Supplementary Information for

An Environmentally Friendly Mukaiyama Aldol Reaction Catalyzed by a Strong Brønsted Acid in Solvent-Free Conditions

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General Information

All the reactions were conducted in vials using analytical grade reagents, and were monitored by TLC, GC and GC-MS spectrometry. GC-MS spectra were recorded with an AT5973N mass selective detector connected to an AT6890N GC cross-linked methyl silicone capillary column. IR spectra were recorded using a Perkin Elmer Spectrum BX FT-IR spectrometer in neat conditions or as solutions in CHCl\(_3\). \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded in CDCl\(_3\) with a Bruker Avance 200 spectrometer at 200 MHz and 50 MHz, respectively; chemical shifts are given in ppm relative to CDCl\(_3\). TLC were performed on Fluka silica gel TLC PET foils GF 254, 2–25 \(\mu\)m, layer thickness 0.2 mm, medium pore diameter 60 \(\AA\). Plates were visualized using UV light (254 nm) or treatment with an appropriate revelatory agent (\(p\)-anisaldehyde), followed by heating. Column flash chromatography was carried out on SiO\(_2\) (particle size 0.032–0.063 mm/230–400 mesh). Petroleum ether refers to the fraction boiling in the range 40–60 \(^\circ\)C and is abbreviated as PE. Commercially available reagents and solvents were purchased from Aldrich and were used without purification or distillation prior to use; Dowex 50X8 ion-exchange resin was purchased from Fluka.

\(o\)-Benzenedisulfonimide (1) was prepared as described in literature.\(^1\) Moisture-sensitive 3 was prepared following literature;\(^2\) flasks and all equipment used for its generation were dried by electric heat gun under Ar; THF was distilled from Na/benzophenone ketyl. Acetal \(\text{13b}\) was prepared following a previously optimized procedure.\(^3\) Details for the reactions and yields for the pure (GC, GC-MS, TLC, \(^1\)H NMR) isolated products are listed in Table 2, 3 and 4. Structure and purity of all the products were confirmed by comparison of their physical and spectral data (IR, MS, \(^1\)H NMR and \(^{13}\)C NMR) with those reported in literature.

General Procedures

General procedure for Mukaiyama aldol reaction:
A mixture of aldehyde 4 (2.0 mmol), trimethylsilyl enol ether 2 (0.68 g, 4.0 mmol) or 3 (0.50 g, 2.6 mmol), and o-benzenedisulfonimide (1, mol % as in Table 2) was stirred at r.t. in a vial until TLC and GC analyses showed almost complete conversion of 4. The reaction mixture was then treated with 2 N HCl (2 mL) and vigorously stirred at rt for 5-20 min. After TLC analyses showed complete hydrolysis of 5 to 6 (or 8 to 9), the mixture was extracted with CH2Cl2 (3x 10 mL). The organic extracts were washed with aqueous NaHCO3 (20 mL), dried with Na2SO4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a short column of silica gel (eluent is reported in footnote of Table 2). Starting from 2, aldols 6 were revealed by treatment of the TLC plates with an appropriate revelatory agent (p-anisaldehyde), followed by heating. The first eluted product was the enone 7, followed by the aldol product 6-syn and then by the anti-diastereomer.

2-[(4-Chlorophenyl)(hydroxy)methyl]cyclohexan-1-one (6a).
White solid, 68% yield; dr (syn/anti) = 50:50, determined by 1H NMR analysis of title compound isolated partially as the pure syn and anti diastereomers, and partially as a mixture.

syn-6a: 1H NMR (200 MHz, CDCl3): δ = 1.13–1.25 (m, 1H), 1.40–1.88 (m, 5H), 1.98–2.10 (m, 1H), 2.30–2.50 (m, 3H), 5.29 (d, J = 2.4 Hz, 1H), 7.12–7.28 (m, 4H); 13C NMR (50 MHz, CDCl3): δ = 24.7, 25.8, 27.7, 42.5, 56.8, 69.9, 127.0 (2C), 128.1 (2C), 132.1, 139.8, 214.4. FT-IR (CHCl3, cm⁻¹): 3584, 3539, 3016, 2946, 2870, 1698, 1494, 1208, 1091, 702.

anti-6a: 1H NMR (200 MHz, CDCl3): δ = 1.11–1.40 (m, 1H), 1.42–1.80 (m, 5H), 1.98–2.10 (m, 1H), 2.15–2.55 (m, 3H), 4.70 (d, J = 8.8 Hz, 1H), 7.14–7.29 (m, 4H). 13C NMR (50 MHz, CDCl3): δ = 24.5, 27.5, 30.5, 42.4, 57.1, 73.8, 128.2 (2C), 128.3 (2C), 133.3, 139.4, 215.1. FT-IR (CHCl3, cm⁻¹): 3584, 3539, 3025, 2946, 2869, 1697, 1491, 1211, 1089, 781.

2-(4-Chlorobenzylidene)cyclohexan-1-one (7a).
Yield 5%. 1H NMR (200 MHz, CDCl3): δ = 1.64–1.74 (m, 2H), 1.78–1.90 (m, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.71 (td, J = 6.4 and 2.2 Hz, 2H), 7.20–7.30 (m, 4H), 7.34 (t, J = 2.2 Hz, 1H).
MS m/z (%): 220 [M⁺](88), 129 (100).

2-[(4-Methoxyphenyl)(hydroxy)methyl]cyclohexan-1-one (6b).
Solid, 68% yield; dr (syn/anti) = 59:41, determined by 1H NMR analysis of title compound isolated partially as pure syn and anti diastereomers, and partially in mixture.

syn-6b: 1H NMR (200 MHz, CDCl3): δ = 1.40–1.80 (m, 5H), 1.95–2.10 (m, 1H), 2.20–2.55 (m, 3H), 2.96 (br s, 1H), 3.74 (s, 3H), 5.26 (br s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H); 13C NMR (50 MHz, CDCl3): δ = 24.7, 26.0, 27.8, 42.5, 55.1, 57.1, 70.2, 113.4 (2C), 126.7 (2C), 133.4, 158.4, 214.7.

anti-6b: 1H NMR (200 MHz, CDCl3): δ = 1.40–1.80 (m, 5H), 1.95–2.10 (m, 1H), 2.20–2.55 (m, 3H), 2.96 (br s, 1H), 3.74 (s, 3H), 5.26 (br s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H); 13C NMR (50 MHz, CDCl3): δ = 24.7, 26.0, 27.8, 42.5, 55.1, 57.1, 70.2, 113.4 (2C), 126.7 (2C), 133.4, 158.4, 214.7.

FT-IR (CHCl₃, cm⁻¹): 3584, 3555, 3027, 2945, 2870, 1697, 1614, 1514, 1250, 768, 668.

**anti-6b.**¹ H NMR (200 MHz, CDCl₃): δ = 1.15–1.25 and 1.42–1.75 (m, 5H), 1.95–2.08 (m, 1H), 2.25–2.60 (m, 4H), 3.74 (s, 3H), 4.68 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ = 24.5, 27.6, 30.6, 42.5, 55.1, 57.3, 74.1, 113.6 (2C), 128.0 (2C), 133.0, 159.1, 215.4.

FT-IR (CHCl₃, cm⁻¹): 3584, 3540, 3016, 2857, 1698, 1604, 1512, 1203, 680, 664.

2-(4-Methoxybenzylidene)cyclohexan-1-one (7b). Yield 16%. ¹H NMR (200 MHz, CDCl₃): δ = 1.15–1.25 and 1.42–1.75 (m, 5H), 1.95–2.08 (m, 1H), 2.25–2.60 (m, 4H), 3.74 (s, 3H), 4.68 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ = 24.5, 27.6, 30.6, 42.5, 55.1, 57.3, 74.1, 113.6 (2C), 128.0 (2C), 133.0, 159.1, 215.4.

2-(Hydroxy)(phenyl)methyl)cyclohexan-1-one (6c). Solid, 51% yield; dr (syn/anti) = 57:43, determined by ¹H NMR analysis of title compound isolated partially as pure syn and anti diastereomers, and partially in mixture.

**syn-6c.**¹ H NMR (200 MHz, CDCl₃): δ = 1.64–1.85 (m, 5H), 1.95–2.10 (m, 1H), 2.25–2.58 (m, 4H), 5.33 (d, J = 2.4 Hz, 1H), 7.18–7.34 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ = 24.7, 25.8, 27.8, 42.5, 57.0, 70.4, 125.6 (2C), 126.8, 128.0 (2C), 141.3, 214.7.

FT-IR (CHCl₃, cm⁻¹): 3684, 3622, 3026, 2977, 2896, 1698, 1605, 1522, 1451, 1208, 787, 664.

**anti-6c.**¹ H NMR in mixture with syn-6c in 2:1 dr syn:anti (200 MHz, CDCl₃) δ = 1.40–1.83 (m, 5H), 1.98–2.10 (m, 1H), 2.23–2.62 (m, 3H), 4.73 (anti; d, J = 8.8 Hz, 1H), 5.33 (syn; br s, 1H), 7.18–7.34 (m, 5H).

MS m/z (%): 216 [M⁺](100).

2-Benzylidenecyclohexan-1-one (7c). Yield 19%. ¹H NMR (200 MHz, CDCl₃): δ = 1.67–1.75 (m, 2H), 1.84–1.90 (m, 2H), 2.48 (t, J = 6.6 Hz, 2H), 2.78 (td, J = 6.4 and 2.2 Hz, 2H), 7.25–7.35 (m, 5H), 7.44 (t, J = 2.2 Hz, 1H).

MS m/z (%): 186 [M⁺](63), 185 (100).

2-(Hydroxy)(4-nitrophenyl)methyl)cyclohexan-1-one (6d). Yellow solid, 48% yield; dr (syn/anti) = 50:50, determined by ¹H NMR analysis of title compound isolated partially as pure syn and anti diastereomers, and partially in mixture.

**syn-6d.**¹ H NMR (200 MHz, CDCl₃): δ = 1.35–1.70 (m, 5H), 1.95–2.10 (m, 1H), 2.23–2.61 (m, 3H), 3.19 (d, J = 3.2 Hz, 1H), 5.41 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 9.0 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ = 24.5, 25.7, 27.6, 42.4, 56.6, 69.9, 123.2 (2C), 126.4 (2C), 146.8, 149.0, 213.9.

FT-IR (CHCl₃, cm⁻¹): 3584, 3545, 3027, 2947, 2871, 1700, 1605, 1522, 1208, 854.

**anti-6d.**¹ H NMR in mixture with syn-6d in 1:1 dr syn:anti (200 MHz, CDCl₃) δ = 1.15–1.83 (m, 6H), 1.95–2.10 (m, 1H), 2.15–2.40 (m, 2H), 2.40–2.60 (m, 1H), 4.83 (anti; d, J = 8.4 Hz, 1H), 5.41 (syn; br s, 1H), 7.35–7.50 (m, 2H), 8.07–8.20 (m, 2H).

FT-IR (CHCl₃, cm⁻¹): 3584, 3545, 3029, 2947, 2870, 1699, 1607, 1525, 1350, 1214, 856.
2-(4-Nitrobenzylidene)cyclohexan-1-one (7d). Yield 15%. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 1.60–2.00 (m, 4H), 2.51 (t, $J$ = 6.6 Hz, 2H), 2.76 (td, $J$ = 6.4 and 2.2 Hz, 2H), 7.35–7.39 (m, 1H), 7.45 (d, $J$ = 8.8 Hz, 2H), 8.17 (d, $J$ = 8.8 Hz, 2H). MS m/z (%): 231 [M$^+$](13), 214 (100).

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\begin{align*}
\text{OH} & \quad \text{CN}
\end{align*}
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2-[(4-Cyanophenyl)(hydroxy)methyl]cyclohexan-1-one (6e). Solid, yield 48%; dr (syn/anti) = 46:54, determined by $^1$H NMR analysis of title compound isolated partially as pure syn and anti diastereomers, and partially in mixture.

**syn-6e:** $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 1.38–1.80 (m, 5H), 1.95–2.10 (m, 1H), 2.20–2.40 (m, 2H), 2.45–2.58 (m, 1H), 3.21 (br s, 1H), 5.33 (d, $J$ = 2.0 Hz, 1H), 7.34 (d, $J$ = 9.6 Hz, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ = 24.6, 25.7, 27.6, 42.4, 56.6, 70.0, 109.8, 126.3 (2C), 130.4, 132.0 (2C), 146.9, 213.9. FT-IR (CHCl$_3$, cm$^{-1}$): 3584, 3545, 3024, 2947, 2871, 2232, 1701, 1604.

**anti-6e:** $^1$H NMR in mixture with syn-6d in 0.8:1 dr syn:anti (200 MHz, CDCl$_3$) $\delta$ = 1.15–1.83 (m, 6H), 1.95–2.05 (m, 1H), 2.15–2.40 (m, 3H), 4.77 (anti; d, $J$ = 8.4 Hz, 1H), 5.36 (syn; br s, 1H), 7.30–7.42 (m, 2H), 7.50–7.61 (m, 2H). FT-IR (CHCl$_3$, cm$^{-1}$): 3584, 3545, 3020, 2931, 2857, 2232, 1682, 1604. 

2-(4-Cyanobenzylidene)cyclohexan-1-one (7e). Yield 14%. $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 1.69–1.80 (m, 2H), 1.83–1.95 (m, 2H), 2.50 (t, $J$ = 6.8 Hz, 2H), 2.70–2.88 (m, 2H), 7.39 (d, $J$ = 8.4 Hz, 2H), 7.48 (s, 1H), 7.60 (d, $J$ = 8.2 Hz, 2H). MS m/z (%): 211 [M$^+$](100).

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\begin{align*}
\text{OH} & \quad \text{CN}
\end{align*}
\]

3-(4-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (9a). White needles, mp 99.4–100.4 °C (CH$_2$Cl$_2$–PE) [lit. 96–96.5 °C]. Yield 87%.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 3.20 (br s, 1H), 3.28 (d, $J$ = 6.0 Hz, 2H), 5.20–5.31 (m, 1H), 7.26–7.32 (m, 4H), 7.35–7.45 (m, 2H), 7.48–7.55 (m, 1H), 7.80–7.93 (m, 2H). $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ = 47.1, 69.2, 127.0 (2C), 128.0 (2C), 128.5 (2C), 128.6 (2C), 133.1, 133.6, 136.2, 141.3, 199.8. FT-IR (CHCl$_3$, cm$^{-1}$): 3584, 3550, 3010, 2905, 1677, 1598, 1582, 1494, 1450, 1093, 1014, 800, 668.

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\begin{align*}
\text{OH} & \quad \text{Cl}
\end{align*}
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3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (9b).\textsuperscript{8,10}

Colorless oil; yield 88%.

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 3.24–3.32\) (m, 2H), 3.50 (br s, 1H), 3.72 (s, 3H), 5.22 (m, 1H), 6.80–6.90 (m, 2H), 7.25–7.60 (m, 5H), 7.84–7.92 (m, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 47.2, 55.1, 69.5, 113.7\) (2C), 126.9 (2C), 128.0 (2C), 128.5 (2C), 133.4, 135.1, 136.5, 158.9, 199.9.

FT-IR (neat, cm\(^{-1}\)): 3480, 3062, 3003, 2907, 2837, 1682, 1513, 1449, 1249, 1034, 833, 724, 691.

MS \(m/z\) (%): 252 [M\(^+\)] (5), 238 [M\(^+\)–18] (100).

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\text{O} \quad \text{OH}
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3-Hydroxy-1,3-diphenylpropan-1-one (9c).\textsuperscript{8,10}

Viscous colorless oil; yield 80%.

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 2.46\) (br s, 1H), 3.32 (d, \(J = 6.2\) Hz, 2H), 5.30 (m, 1H), 7.20–7.45 (m, 7H), 7.50–7.56 (m, 1H), 7.80–7.95 (m, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 47.3, 69.9, 125.6, 127.5, 128.0, 128.4, 133.5, 136.4, 142.8, 200.0\).

FT-IR (CDCl\(_3\), cm\(^{-1}\)): 3584, 3545, 3035, 3011, 2905, 1677, 1599, 1496, 1450, 778, 691, 668.

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\text{O} \quad \text{OH}
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3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (9d).\textsuperscript{8,10}

White needles, mp 114.0–114.7 °C (CH\(_2\)Cl\(_2\)–PE) [lit.\textsuperscript{10} 113–114 °C]. Yield 91%.

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 3.26–3.36\) (m, 2H), 3.82 (br s, 1H), 5.35–5.44 (m, 1H), 7.35–7.48 (m, 2H), 7.50–7.60 (m, 3H), 7.85–7.92 (m, 2H), 8.14–8.20 (m, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 46.8, 69.0, 123.6\) (2C), 126.4 (2C), 128.0 (2C), 128.7 (2C), 133.9, 135.9, 147.1, 150.0, 199.3.

FT-IR (CDCl\(_3\), cm\(^{-1}\)): 3584, 3550, 2907, 3024, 1677, 1600, 1582, 1524, 1450, 1350, 1208, 736, 670.

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\text{O} \quad \text{OH} \quad \text{NO}_2
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3-(4-Cyanophenyl)-3-hydroxy-1-phenylpropan-1-one (9e).\textsuperscript{11}

White needles, mp 86.0–87.0 °C (CH\(_2\)Cl\(_2\)–PE). Yield 96%.

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 3.20–3.32\) (m, 2H), 3.75 (br s, 1H), 5.25–5.38 (m, 1H), 7.30–7.60 (m, 2H), 7.80–7.90 (m, 2H); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)): \(\delta = 46.9, 69.1, 111.1, 118.6, 126.3\) (2C), 128.0 (2C), 128.6 (2C), 132.5 (2C), 133.8, 136.0, 148.3, 199.3.

FT-IR (CDCl\(_3\), cm\(^{-1}\)): 3584, 3550, 3030, 2906, 2233, 1678, 1598, 1581, 1450, 1231, 1210, 798, 727.

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\text{O} \quad \text{OH} \quad \text{CN}
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3-Hydroxy-1-phenyl-3-(2-tolyl)propan-1-one (9f). Colorless oil; yield 98%.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta = 2.31$ (s, 3H), 3.24-3.30 (m, 2H), 3.57 (br s, 1H), 5.50-5.58 (m, 1H), 7.12–7.24 (m, 3H), 7.35–7.60 (m, 4H), 7.88–7.98 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta =$ 19.0, 46.0, 66.3, 125.4, 126.3, 127.3, 128.0 (2C), 128.6 (2C), 130.3, 133.5, 133.9, 136.4, 140.9, 200.1

FT-IR (neat, cm$^{-1}$): 3469, 3063, 2923, 1682, 1598, 1580, 1490, 1450, 1212, 1065, 760, 691.

3-Hydroxy-1-phenyl-3-(2-trifluoromethylphenyl)propan-1-one (9g). Colorless oil; yield 80%.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta =$ 3.10-3.40 (m, 2H), 2.89 (br s, 1H), 5.70-5.78 (m, 1H), 7.30–7.65 (m, 6H), 7.84–7.95 (m, 3H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta =$ 47.3, 65.4, 125.3 (q, $J = 6.6$ Hz), 126.2 (q, $J = 30.0$ Hz), 127.5, 127.7, 128.0 (2C), 128.5 (2C), 129.5 (q, $J = 265$ Hz), 132.3, 133.6, 136.1, 141.8, 199.5.

FT-MS m/z (%): 294 [M$^+$] (5), 276 [M$^+$–18] (20), 105 (100).

IR (neat, cm$^{-1}$): 3480, 3069, 2915, 1682, 1598, 1582, 1493, 1451, 1308, 1166, 1060, 1037, 771.

3-Hydroxy-1-phenyl-3-(2-thienyl)propan-1-one (9h). Viscous oil, yield 89%.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta =$ 3.35-3.46 (m, 2H), 3.93–3.99 (m, 1H), 5.45-5.55 (m, 1H), 6.88–6.98 (m, 2H), 7.15–7.20 (m, 1H), 7.35–7.55 (m, 3H), 7.83–7.91 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta =$ 47.1, 66.2, 123.5, 124.5, 126.6, 128.1, 128.6, 133.6, 136.3, 146.8, 199.3.

FT-IR (neat, cm$^{-1}$): 3468, 3067, 2904, 1678, 1597, 1580, 1449, 1212, 1040, 759, 693.

(E)-3-Hydroxy-1,5-diphenylpent-4-en-1-one (9i). White solid, mp 53.2–54.1 °C (CH$_2$Cl$_2$/PE) [lit. 52.1-52.9 °C]; yield 80%.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta =$ 3.23 (d, $J = 6.0$ Hz, 2H), 3.49 (br s, 1H), 4.85–4.93 (m, 1H), 6.27 (dd, $J = 15.8$ and 6 Hz, 1H), 6.66 (d, $J = 16.0$ Hz, 1H), 7.20–7.55 (m, 8H), 7.90–7.95 (m, 2H); $^{13}$C

NMR (50 MHz, CDCl₃): δ = 45.1, 68.5, 126.4, 127.5, 128.0, 128.4, 128.5, 130.2, 130.3, 133.5, 136.4, 136.5, 199.8.

FT-IR (CHCl₃, cm⁻¹): 3584, 3545, 3011, 2904, 1678, 1599, 1585, 1450, 1215, 704.

5-Oxo-3,5-diphenylpentanal (10).¹³,¹⁴
Colorless oil; yield 16%.
¹H NMR (200 MHz, CDCl₃): δ = 2.77–2.84 (m, 2H), 3.27–3.32 (m, 2H), 3.84–3.98 (m, 1H), 7.20–7.50 (m, 8H), 7.82–7.90 (m, 2H), 9.65 (s, 1H); ¹³C NMR (50 MHz, CDCl₃): δ = 35.2, 44.8, 49.4, 126.8, 127.2, 127.9, 128.5, 128.7, 133.1, 136.6, 143.0, 197.9, 201.0.

FT-IR (CHCl₃, cm⁻¹): 3584, 3535, 3035, 2965, 2940, 1722, 1677, 1599, 1582, 1450, 1234, 1214, 1181.

MS m/z (%): 252 [M +] (5), 105 (100).

3-Hydroxy-1-phenyloctan-1-one (12).¹⁵
Viscous colorless oil; yield 32%.
¹H NMR (200 MHz, CDCl₃): δ = 0.77–0.90 (m, 3H), 1.18–1.60 (m, 8H), 2.89–2.20 (m, two dd overlapped and one br s, 3H), 4.11–4.20 (m, 1H), 7.34–7.55 (m, 3H), 7.82–7.95 (m, 2H); ¹³C NMR (50 MHz, CDCl₃): δ = 13.9, 22.5, 25.1, 31.6, 36.3, 44.8, 67.6, 127.9, 128.5, 133.3, 136.6, 200.9.

FT-IR (CHCl₃, cm⁻¹): 3584, 3545, 3009, 2905, 2861, 1677, 1599, 1582, 1450, 1234, 1214, 1181.

MS m/z (%): 220 [M +] (5), 206 [M +–18] (25), 105 (100).

Synthesis of cyclohexanecarbaldehyde dimethyl acetal (13b):
Title compound was prepared following a previously optimized procedure.³ To a solution of cyclohexanecarbaldehyde (1.12 g, 10 mmol) in methanol (10 mL) was added o-benzenedisulfonimide (1; 0.5 mol%; 0.011 g, 0.05 mmol) and the reaction mixture was stirred at r.t. for 1h. The reaction mixture was treated with pentane and NaHCO₃, extracted with pentane (3 x 10 mL) and evaporated under reduced pressure. The residue was virtually pure (GC, GC–MS, TLC, ¹H NMR and ¹³C NMR) title compound in 99 % yield (1.56 g); colorless oil.¹⁶ Traces of a trimer of cyclohexane carbaldehyde were detected; GC-MS: 335 ([M+-1] 5), 225 (70), 113 (85), 95 (100).
¹H NMR (200 MHz, CDCl₃): δ = 1.48–1.72 (m, 6H), 0.80–1.20 (m, 5H), 3.25 (s, 6H), 3.91 (d, J = 7.2 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃): δ = 25.6, 26.2, 27.8, 39.8, 53.3, 108.3.

MS m/z (%): 157 [M+-1](5), 75 (100).

General procedure for Mukaiyama aldol-type reaction:

A mixture of aldehyde dimethyl acetal 13 (2.0 mmol), trimethylsilyl enol ether 3 (0.50 g, 2.6 mmol), and o-benzenedisulfonimide (1, mol % as in Table 3) was stirred at r.t. in a vial until TLC and GC analyses showed almost complete conversion of 13. The mixture was extracted with CH₂Cl₂, washed with water and then extracted with CH₂Cl₂ (3 x 10 mL). The organic extracts were dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a short column of silica gel (eluent reported in footnote of Table 3).

![Chemical Structure](image)

3-Methoxy-1-phenyloctan-1-one (14a).
Colorless oil; yield 81%.

1H NMR (200 MHz, CDCl₃): δ = 0.70–0.85 (m, 3H), 1.20–1.05 (m, 6H), 1.45–1.60 (m, 2H), 2.86 (dd, J₁ = 16.2 and 5.4 Hz, 1H), 2.86 (overlapped dd, J₂ = 16.0 and 6.8 Hz, 1H), 3.26 (s, 3H), 3.75–3.85 (m, 1H), 7.35–7.50 (m, 3H), 7.85–7.93 (m, 2H); 13C NMR (50 MHz, CDCl₃): δ = 13.9 22.4, 24.7, 31.7, 34.2, 43.1, 57.0, **77.7**, 128.0 (2C), 128.4 (2C), 132.8, 137.2, 198.9.

FT-IR (neat, cm⁻¹): 3062, 2930, 2860, 1686, 1598, 1581, 1449, 1364, 1282, 1212, 1097, 753, 659.

MS m/z (%): 234 [M⁺] (2), 219 [M⁺-15] (10), 105 (100).

3-Cyclohexyl-3-methoxy-1-phenylpropan-1-one (14b).10
Colorless oil, 61% yield.

1H NMR (200 MHz, CDCl₃): δ = 0.90–1.18 (m, 5H), 1.45–1.72 (m, 6H), 2.84 (dd, J₁ = 16.2 and 4.0 Hz, 1H), 3.13 (overlapped dd, J₂ = 16.2 and 7.8 Hz, 1H), 3.23 (s, 3H), 3.59–3.68 (m, 1H), 7.32–7.46 (m, 3H), 7.85–7.92 (m, 2H); 13C NMR (50 MHz, CDCl₃): δ = 26.1 (2C), 26.4, 28.3, 28.4, 40.6, 41.7, 58.1, 81.6, 128.0 (2C), 128.3 (2C), 132.7, 137.3, 199.2.

FT-IR (CHCl₃, cm⁻¹): 3013, 2905, 2856, 1684, 1598, 1582, 1450, 1232, 1095.

MS m/z (%): 246 [M⁺] (2), 231 [M⁺-15] (10), 105 (100).

3-Methoxy-1,4-diphenylbutan-1-one (14c).17
Colorless viscous oil; yield 33%.

1H NMR (200 MHz, CDCl₃): δ = 2.80–2.91 (m, 3H), 3.18 (dd, J₁ = 16.4 and 7.2 Hz, 1H), 3.28 (s, 3H), 4.05–4.11 (m, 1H), 7.15–7.25 (m, 5H), 7.39–7.50 (m, 3H), 7.83 (d, J₂ = 7.8 Hz, 2H); 13C NMR (50 MHz, CDCl₃): δ = 40.0, 42.6, 57.4, 78.4, 124.3, 128.0 (2C), 128.4 (2C), 128.7 (2C), 129.4 (2C), 132.9, 137.0, 138.0, 198.6.

FT-IR (neat, cm⁻¹): 3063, 3029, 2932, 2830, 1683, 1599, 1582, 1496, 1450, 1360, 1266, 1121, 760, 691.

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MS \textit{m/z} (%): 239 \textit{[M$_{+}$-15]} (2), 105 (100).

\textbf{Mechanistic studies:}

\textbf{A) Mukaiyama aldol reaction in the presence of a hindered base:}\textsuperscript{18,19}
A mixture of trimethylsilyl enol ether 3 (0.50 g, 2.6 mmol), 2,6-di(t-buty1)-4-methylpyridine (5 mol \%, 0.0205 g) and \textit{o}-benzenedisulfonimide (1, 2 mol \%, 0.0088 g) was stirred at r.t. in a vial; after 5 min aldehyde 4f (0.24 g; 2.0 mmol) was added. The reaction was suspended after 24 h. Acid hydrolysis and usual work-up followed by flash chromatography gave 9f (0.40 g; 83\%; entry 1 of Table 4).

\textbf{B) Mukaiyama aldol reaction catalyzed by \textit{in situ} formed Lewis catalyst:}\textsuperscript{18,19}
Reactions were carried out on 2 mmol of reactants, as usual.
A mixture of trimethylsilyl enol ether 2 or 3 (2 mol \%) and one equivalent of 1 was stirred at r.t. in a vial: \textsuperscript{1}H NMR spectra showed the formation of N-trimethylsilyl-o-benzenedisulfonimide and TLC analysis showed complete disappearance of the silyl enol ether. Then reactants 2 and 4b (or 3 and 4f) were added and the reactions were run as in the general procedure. Both reactions proceeded in a similar fashion. In both cases, hydrolysis of 2 (or 3) was faster than the expected Mukaiyama reaction. The reactions reached completion in reduced times and yields with respect to the optimized procedures, as reported in entries 2 and 3 of Table 4.

(syn)-2-[(4-Chlorophenyl)(hydroxy)methyl]cyclohexan-1-one (6a).
(anti)-2-[(4-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (6a).
(syn)-2-[(4-Methoxyphenyl)(hydroxy)methyl]cyclohexan-1-one (6b).
(anti)-2-[(4-Methoxyphenyl)(hydroxy)methyl]cyclohexan-1-one (6b).
(syn)-2-[(Hydroxy)(phenyl)methyl]cyclohexan-1-one (6c).
2-[(Hydroxy)(phenyl)methyl]cyclohexan-1-one (6c).
(syn)-2-[(Hydroxy)(4-nitrophenyl)methyl]cyclohexan-1-one (6d).
2-[(Hydroxy)(4-nitrophenyl)methyl]cyclohexan-1-one (6d).
(syn)-2-[(Hydroxy)(4-cyanophenyl)methyl]cyclohexan-1-one (6e).
2-[(Hydroxy)(4-cyanophenyl)methyl]cyclohexan-1-one (6e).
3-(4-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (9a).
3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (9b).
3-Hydroxy-1,3-diphenylpropan-1-one (9c).
3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (9d).\textsuperscript{8,9,6}
3-(4-Cyanophenyl)-3-hydroxy-1-phenylpropan-1-one (9e).
3-Hydroxy-3-(2-tolyl)-1-phenylpropan-1-one (9f).
3-Hydroxy-1-phenyl-3-(2-trifluoromethylphenyl)propan-1-one (9g).
3-Hydroxy-3-(2-thienyl)-1-phenylpropan-1-one (9h).
(trans)-3-Hydroxy-1,5-diphenylpent-4-en-1-one (9i).
5-Oxo-3,5-diphenylpentanal (10)
3-Hydroxy-1-phenyloctan-1-one (12).
Cyclohexanecarbaldehyde dimethyl acetal (13b)
3-Methoxy-1-phenyloctan-1-one (14a).
3-Cyclohexyl-3-methoxy-1-phenylpropan-1-one (14b).