Supporting information

Solvent Strategy for Unleashing Lewis Acidity of Titanocene Dichloride for Rapid Mannich Reactions

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1. General procedures

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker EQUINX55 (400 MHz for $^1$H; 101 MHz for $^{13}$C) spectrometer in CDCl$_3$. For $^1$H NMR, tetramethylsilane (TMS) served as internal standard ($\delta = 0$) and $^1$H NMR chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak (CDCl$_3$ at 7.26 ppm) unless otherwise noted. The data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), and coupling constant in Hz. For $^{13}$C NMR, CDCl$_3$ was used as internal standard ($\delta = 77.0$) and spectra were obtained with complete proton decoupling. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR spectrometer and reported as wavenumbers (cm$^{-1}$). 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 stained with an iodine vapor.

2. Typical procedures for three-component Mannich reactions

A nitrogen flushed 10 mL test tube, equipped with a magnetic stirrer and a septum, was charged with methanol (0.5 mL), benzaldehyde (1.0 mmol), aniline (1.0 mmol), and the aromatic/aliphatic ketone (2.0 mmol) in one portion. Cp$_2$TiCl$_2$ (0.01 mmol) was added at 25 °C and stirred until the reaction was completed as indicated by TLC. Upon completion of the reaction, the reaction mixture was quenched with distilled water (5.0 mL). The aqueous phase was extracted with ether (3×5 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to give desired products. The crude product was purified by flash column chromatography on neutral silica gel (ethyl acetate: n-hexane).

3. NMR experiments

The interplay of Cp$_2$TiCl$_2$ and methanol was investigated by $^1$H NMR in mechanistic scenario (Figure S1). A general procedure was as follows: Cp$_2$TiCl$_2$ (10 μmol) was placed in CD$_3$OD (0.5mL) and the solution was detected immediately as observed by $^1$H NMR spectroscopy. The mixture was allowed to stand for 1 h and was conducted by $^1$H NMR spectroscopy as confirmed by $^1$H NMR spectroscopy. After 1.0 equiv. of aniline was added in the above solution, one new Cp protons singlet appeared at $\delta$ 6.70 ppm. Titanocene chloride (I) was consumed gradually in CD$_3$OD in the presence of base and formed new titanocene species Cp$_2$Ti(OCH$_3$)$_2$ (II) (Scheme S1).
Scheme S1. The coordination of Cp₂TiCl₂ with CH₃OH unleashed Lewis acidity and Brønsted acidity by ¹H NMR and ESI-MS.

Figure S1. Partial 400MHz ¹H NMR spectra (CD₃OD) of a solution containing Cp₂TiCl₂ with addition of aniline.

4. Spectrometric analysis

Mass spectrometric measurements were performed in a Bruker EVOQ tandem mass spectrometer. As a general rule, scan mode was Q1MS, positive ion mode (otherwise indicated), tube lens potential was optimized in each case or for a series of measurements that required equal conditions, a time span of 1 minute was used to collect spectra and average them. The tube lens potential was adjusted in a way that the most interest ions had almost no attenuation (around 70 V).
For CID experiments, the cations of interest were mass-selected using the first quadrupole (Q1) and interacted with argon in the T-wave collision cell at variable collision energies (Elaboratory= 3-15 eV). The ionic products of fragmentation were analyzed with the time-of-flight analyzer. The isolation width was 1Da and the most abundant isotopomer was mass-selected in the first quadrupole analyzer.

5. Characterization data of products

4a

1,3-Diphenyl-3-(N-phenylamino)propan-1-one (4a): Yield, 95%; white solid; mp 170-172 °C; Rf 0.51 (hexane/ethyl acetate = 4:1); IR (KBr): 3383, 1669; HRMS (ESI) m/z 302.1498 [C_{21}H_{19}NO (M+1) requires 302.1545]; 1H NMR (400 MHz, CDCl₃) δ 7.89-7.91 (m, 2H), 7.56 (dd, J = 10.5, 4.3, 1H), 7.45 (dd, J = 10.5, 4.5, 4H), 7.32 (t, J = 7.5, 2H), 7.23 (t, J = 7.3, 1H), 7.06-7.09 (m, 2H), 6.68 (t, J = 7.3, 1H), 6.56-6.59 (m, 2H), 5.02 (dd, J = 7.4, 5.4, 1H), 3.48 (qd, J = 16.1, 6.4, 2H); 13C NMR (101 MHz, CDCl₃) δ 198.26, 146.78, 142.81, 136.76, 133.40, 129.11, 128.82, 128.69, 128.20, 127.39, 126.43, 118.02, 114.04, 55.03, 46.21.

4b

3-[N-(4-Methylphenylamino)]-1,3-diphenylpropan-1-one (4b): Yield, 95%; white solid; mp 125-126 °C; Rf 0.45 (hexane/ethyl acetate = 4:1); IR (KBr): 3376, 1674; HRMS (ESI) m/z 316.1689 [C_{22}H_{21}NO (M+1) requires 316.1701]; 1H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.43 (m, 4H), 7.31 (t, J = 7.5 Hz, 2H), 7.24 (m, 1H), 6.89 (d, J = 8.1 Hz, 2H), 6.48 (d, J = 8.2 Hz, 2H), 4.97 (m, 1H), 4.40 (s, 1H), 3.45 (ddd, J = 23.7, 16.1, 6.4 Hz, 2H), 2.17 (s, 3H); 13C NMR (101 MHz, CDCl₃) δ 198.32, 144.71, 143.17, 136.80, 133.34, 129.59, 128.78, 128.66, 128.19, 127.28, 127.00, 126.39, 114.03, 55.11, 46.36, 20.33.
3-[N-(4-chlorophenylamino)]-1,3-diphenylpropan-1-one (4c): Yield, 85%; yellowish solid; mp 167-168 °C; Rf 0.40 (hexane/ethyl acetate = 4:1); IR (KBr): 3370, 1665; HRMS (ESI) m/z 336.1140 [C_{21}H_{18}ClNO (M+1) requires 336.1155]; ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 7.8, 2H), 7.56 (t, J = 7.3, 1H), 7.42-7.44 (m, 4H), 7.32 (t, J = 7.5, 2H), 7.24 (s, 1H), 7.02 (d, J = 8.7, 2H), 6.47 (d, J = 8.7, 2H), 4.93-4.96 (m, 1H), 3.37-3.47 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 198.16, 145.58, 142.51, 136.65, 133.51, 128.92, 128.90, 128.73, 128.19, 127.50, 126.29, 122.48, 114.98, 54.95, 46.20.

3-(4-Methoxyphenyl)-1-phenyl-3-(N-phenylamino)propan-1-one (4d): Yield, 96%; white solid; mp 150-151 °C; Rf 0.32 (hexane/ethyl acetate = 4:1); IR (KBr): 3374, 1664; HRMS (ESI) m/z 332.1647 [C_{22}H_{21}NO₂ (M+1) requires 332.1650]; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, J = 7.3, 2H), 7.53 (t, J = 7.4, 1H), 7.41 (t, J = 7.7, 2H), 7.35 (d, J = 8.6, 2H), 7.09 (t, J = 7.9, 2H), 6.83 (d, J = 8.7, 2H), 6.71 (t, J = 7.3, 1H), 6.63 (d, J = 7.8, 2H), 4.97 (t, J = 6.4, 1H), 3.74 (s, 3H), 3.49-3.56 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 198.16, 158.98, 145.81, 136.78, 134.04, 133.36, 129.15, 128.67, 128.20, 127.79, 118.87, 114.90, 114.21, 55.28, 55.24, 45.86.

3-(4-Chlorophenyl)-1-phenyl-3-(N-phenylamino)propan-1-one (4e): Yield, 88%; white solid; mp 114-115 °C; Rf 0.39 (hexane/ethyl acetate = 4:1); IR (KBr): 3398, 1676; HRMS (ESI) m/z 336.1140
[C$_2$H$_{18}$NOCl (M+1) requires 336.1155]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 8.0$, 2H), 7.52-7.54 (m, 1H), 7.41 (t, $J = 7.6$, 2H), 7.35 (d, $J = 8.2$, 2H), 7.22-7.25 (m, 2H), 7.06 (t, $J = 7.6$, 2H), 6.65 (t, $J = 7.2$, 1H), 6.51 (d, $J = 8.3$, 2H), 4.95 (t, $J = 6.3$, 1H), 4.54 (s, 1H), 3.40-3.43 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.91, 146.74, 141.56, 136.63, 133.56, 132.99, 129.17, 128.97, 128.77, 128.18, 127.86, 118.09, 113.89, 54.21, 46.11.

3-(2-Chlorophenyl)-1-phenyl-3-[ N-(phenylamino)propan-1-one (4f): Yield, 74%; white solid; mp 52-53 °C; Rf 0.48 (hexane/ethyl acetate = 5:1); IR (KBr): 3402, 1675; HRMS (ESI) m/z 336.1156 [C$_2$H$_{18}$ClNO (M+1) requires 336.1155]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (d, $J = 8.0$ Hz, 2H), 7.54 (dd, $J = 10.6$, 6.8 Hz, 2H), 7.42-7.44 (m, 3H), 7.15-7.17 (m, 2H), 7.07 (t, $J = 7.8$ Hz, 2H), 6.64 (t, $J = 7.3$ Hz, 1H), 6.47 (d, $J = 8.5$ Hz, 2H), 5.30 (d, $J = 5.0$ Hz, 1H), 4.90 (s, 1H), 3.61 (dd, $J = 15.5$, 3.9 Hz, 1H), 3.29 (dd, $J = 15.5$, 8.7 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.49, 145.48, 138.52, 135.50, 132.51, 131.34, 128.80, 128.08, 127.69, 127.51, 127.33, 127.09, 126.41, 116.86, 112.60, 51.01, 42.74.

3-(4-nitrophenyl)-1-phenyl-3-(phenylamino)-1-propanone (4g): Yield, 75%; yellow solid; mp 154-156 °C; Rf 0.32 (hexane/ethyl acetate = 5:1); IR (KBr): 3402, 1675; HRMS (ESI) m/z 347.1214[C$_2$H$_{18}$N$_2$O$_3$ (M+1) requires 347.1396]; $\delta$ $^1$H (400 MHz, CDCl$_3$) 8.08 (d, $J = 8.7$ Hz, 2H), 7.87-7.78 (m, 2H), 7.58-7.47 (m, 3H), 7.37 (t, $J = 7.7$ Hz, 2H), 7.02 (t, $J = 7.9$ Hz, 2H), 6.62 (t, $J = 7.3$ Hz, 1H), 6.44 (d, $J = 7.8$ Hz, 2H), 5.03 (s, 1H), 4.61 (s, 1H), 3.43 (d, $J = 6.2$ Hz, 2H); $\delta$ $^{13}$C (101 MHz, CDCl$_3$) 197.3, 150.8, 147.2, 146.3, 136.4, 133.8, 129.3, 128.9, 128.2, 127.5, 124.1, 118.5, 113.9, 77.4, 77.1, 76.8, 54.2, 45.7.
3-[(4-Nitrophenylamino)]- 3-(4-Chlorophenyl)-1-phenylpropan-1-one (4h): Yield: 81%; yellow solid; mp 137-138 °C; Rf 0.25 (hexane/ethyl acetate = 4:1); IR (KBr): 3369, 1687; HRMS (ESI) m/z 381.1117 [C_{21}H_{17}ClN_{2}O_{3} (M+1) requires 381.1106]; ^1H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 9.1 Hz, 2H), 7.88 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.32 (q, J = 8.6 Hz, 4H), 6.50 (d, J = 9.1 Hz, 2H), 5.08 (t, J = 6.0 Hz, 1H), 3.51 (m, 2H); ^13C NMR (101 MHz, CDCl₃) δ 197.53, 151.91, 139.68, 138.80, 136.32, 133.92, 133.70, 129.29, 128.87, 128.16, 127.62, 126.16, 112.28, 53.80, 45.25.

1-(4-Methoxyphenyl)-3-phenyl-3-(N-phenylamino)propan-1-one (4i): Yield, 90%; white solid; mp 123-124 °C; Rf 0.42 (hexane/ethyl acetate = 4:1); IR (KBr): 3383, 1659; HRMS (ESI) m/z 332.1650 [C_{22}H_{21}NO_{2} (M+1) requires 332.1651]; ^1H NMR (400 MHz, CDCl₃) δ 7.81 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 7.4 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.16 (dd, J = 13.4, 6.1 Hz, 1H), 7.00 (dd, J = 8.4, 7.5 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.57 (t, J = 7.3 Hz, 1H), 6.47 (d, J = 7.7 Hz, 2H), 4.89 (dd, J = 7.6, 5.1 Hz, 1H), 4.53 (s, 1H), 3.78 (s, 3H), 3.24-3.40 (m, 2H); ^13C NMR (101 MHz, CDCl₃) δ 196.77, 163.77, 147.10, 143.18, 130.56, 129.85, 129.07, 128.80, 127.28, 126.36, 117.69, 113.85, 113.82, 55.50, 55.06, 46.00.

3-(4-Nitrophenyl)-1-phenyl-3-(N-phenylamino)propan-1-one (4j): Yield, 81%; yellow solid; mp 121-122 °C; Rf 0.21 (hexane/ethyl acetate = 4:1); IR (KBr): 3403, 1674; HRMS (ESI) m/z 347.1399
[C$_2$H$_8$N$_2$O$_3$ (M+1) requires 347.1396]; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (d, $J = 8.6$, 2H), 8.00 (d, $J = 8.6$, 2H), 7.42-7.44 (m, 2H), 7.32 (t, $J = 7.4$, 2H), 7.22-7.25 (m, 1H), 7.11 (t, $J = 7.7$, 2H), 6.71 (t, $J = 7.3$, 1H), 6.60 (d, $J = 8.0$, 2H), 5.04 (t, $J = 6.3$, 1H), 3.55 (d, $J = 5.7$, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 196.83, 150.42, 146.45, 142.03, 141.12, 129.24, 129.16, 128.96, 127.73, 126.41, 123.88, 118.49, 114.13, 54.90, 46.47.

4k

1,3-diphenyl-3-[N-(2-Chlorophenylamino)]propan-1-one (4k): Yield, 76%; white solid; mp 77-78 °C; Rf 0.50 (hexane/ethyl acetate = 4:1); IR (KBr): 3478, 3554, 3413, 1620; HRMS (ESI) m/z 336.1150 [C$_2$H$_{18}$ClNO (M+1) requires 336.1155]; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.90-7.92 (m, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.41-7.44 (m, 4H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.21-7.25 (m, 2H), 6.95-6.99 (m, 1H), 6.58 (td, $J = 7.7$, 1.3 Hz, 1H), 6.51 (dd, $J = 8.2$, 1.2 Hz, 1H), 5.15 (s, 1H), 5.09 (t, $J = 6.3$ Hz, 1H), 3.52 (d, $J = 6.1$ Hz, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 196.72, 141.80, 141.36, 135.78, 132.40, 128.03, 127.86, 127.68, 127.18, 126.60, 126.48, 125.28, 118.59, 116.67, 111.69, 53.48, 45.42.

4l

3-(4-Methoxyphenyl)-1-phenyl-3-(N-phenylamino)propan-1-one (4l): Yield, 85%; white solid; mp 56-57 °C; Rf 0.43 (hexane/ethyl acetate = 4:1); IR (KBr): 3403, 1682; HRMS (ESI) m/z 332.1643 [C$_2$H$_{21}$NO$_2$ (M+1) requires 332.1650]; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.88-7.91 (m, 2H), 7.41-7.43 (m, 1H), 7.30-7.34 (m, 3H), 7.12 (dd, $J = 12.8$, 4.7 Hz, 1H), 6.96 (dd, $J = 8.4$, 7.4 Hz, 2H), 6.80 (m, 2H), 6.53 (d, $J = 7.3$ Hz, 1H), 6.43 (d, $J = 7.7$ Hz, 2H), 5.18 (dd, $J = 8.4$, 4.5 Hz, 1H), 3.85 (s, 3H), 3.55 (dd, $J = 15.1$, 4.5 Hz, 1H), 3.13 (dd, $J = 15.2$, 8.4 Hz, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 199.08, 156.59, 147.10, 136.77, 133.26, 130.06, 129.06, 128.61, 128.58, 128.42, 128.27, 127.65, 121.01, 117.50, 113.73, 110.55, 55.39, 50.71, 44.53.
2-[[4-(methylphenyl)amino]phenylmethyl]-cyclohexanone (4m): Yield, 88%; white solid; Rf 0.48 (hexane/ethyl acetate = 4:1); IR (KBr): 3380, 1697; HRMS (ESI) m/z 294.1837 [C20H23NO (M+1) requires 294.1859]; Major isomer: "H NMR (400 MHz, CDCl3) 7.38 (2 H, t, J = 7.4, ArH), 7.34-7.28 (2 H, m, ArH), 7.23 (1 H, dd, J1 = 10.5, J2 = 3.9, ArH), 6.91 (2 H, dd, J1 = 7.9, J2 = 5.8, ArH), 6.50 (2 H, t, J = 8.4, ArH), 4.81 (0.38 H, d, J = 4.4, syn-CH), 4.63 (0.62 H, d, J = 7.2, anti-CH), 4.52 (1 H, br, NH), 2.83-2.72 (1 H, m, CH), 2.47-2.40 (1 H, m, CH3), 2.35 (1 H, dd, J1 = 13.1, J2 = 5.1, CH2), 2.20 (3 H, d, J = 4.9, CH3), 2.10-2.00 (1 H, m, CH2), 1.88 (3 H, m, CH2), 1.76-1.66 (2 H, m, CH2). 13C NMR (101 MHz, CDCl3) 212.86, 211.39, 145.27, 144.98, 141.92, 141.80, 129.59, 129.55, 128.47, 128.37, 127.55, 127.33, 127.14, 126.96, 126.86, 126.69, 114.31, 113.84, 58.25, 57.61, 57.56, 56.71, 42.43, 41.72, 31.20, 28.69, 27.90, 27.07, 24.88, 23.63, 20.39, 20.36.

2-[[4-(nitrophenyl)amino]phenylmethyl]-cyclohexanone (4n): Yield, 81%; yellow solid; Rf 0.40 (hexane/ethyl acetate = 4:1); IR (KBr): 3374, 1705; HRMS (ESI) m/z 325.1528 [C19H20N2O3 (M+1) requires 325.1552]; Major isomer: "H NMR (400 MHz, CDCl3) 7.98 (2 H, d, J = 9.2, ArH), 7.32 (4 H, d, J = 4.3, ArH), 7.25 (1 H, d, J = 5.4, ArH), 6.49 (2 H, d, J = 9.2, ArH), 5.75 (0.13 H, d, J = 7.6, anti-NH), 5.59 (0.85 H, d, J = 7.1, syn-NH), 4.86 (0.87 H, dd, J1 = 7.2, J2 = 4.4, syn-CH), 4.65 (0.13 H, m, anti-CH), 2.86 (1 H, dt, J1 = 9.5, J2 = 4.6, CH), 2.37 (2 H, m, CH2), 2.05 (2 H, dd, J1 = 15.6, J2 = 9.6, CH2), 1.90 (1 H, d, J = 6.9, CH3), 1.59 (3 H, m, CH3). 13C NMR (101 MHz, CDCl3) 212.50, 211.07, 152.77, 152.66, 140.23, 139.72, 138.24, 138.20, 128.76, 128.69, 127.68, 127.65, 127.45, 126.98, 126.20, 126.14, 112.22, 111.98, 58.12, 57.12, 56.90, 55.61, 42.46, 42.28, 32.32, 28.69, 28.09, 26.59, 24.69, 24.34.
2-[(4-chlorophenyl)(phenylamino)methyl]-cyclohexanone (4o): Yield, 85%; yellow solid; Rf 0.45 (hexane/ethyl acetate = 4:1); IR (KBr): 3386, 1696; HRMS (ESI) m/z 314.1330 [C_{19}H_{20}NOCl (M+1) requires 314.1312]; Major isomer: $^1$H NMR (400 MHz, CDCl$_3$): 7.91 (2 H, d, $J = 9.1$, ArH), 7.21 (5 H, d, $J = 1.6$, ArH), 6.40 (2 H, d, $J = 9.2$, ArH), 5.65 (0.42 H, d, $J = 7.6$, anti-NH), 5.53 (0.58 H, d, $J = 7.2$, syn-NH), 4.71 (0.58 H, dd, $J_1 = 7.1$, $J_2 = 4.6$, syn-CH), 4.55 (0.42 H, dd, $J_1 = 7.4$, $J_2 = 5.6$, anti-CH), 2.78 (1 H, m, CH), 2.30 (2 H, m, CH$_2$), 1.90 (4 H, d, $J = 51.2$, CH$_2$), 1.62 (2 H, dd, $J_1 = 20.9$, $J_2 = 10.2$, CH$_2$). $^{13}$C NMR (101 MHz, CDCl$_3$): 211.16, 209.94, 151.49, 151.29, 137.85, 137.55, 137.50, 137.30, 132.48, 132.42, 127.99, 127.92, 127.85, 127.37, 125.20, 125.13, 111.23, 110.99, 56.69, 55.91, 55.79, 54.39, 41.60, 41.30, 31.44, 28.03, 27.01, 25.56, 23.70, 23.53.

2-[(4-nitrophenyl)(phenylamino)methyl]-cyclohexanone (4p): Yield, 72%; yellow solid; Rf 0.41 (hexane/ethyl acetate = 4:1); IR (KBr): 3374, 1701; HRMS (ESI) m/z 325.1520 [C$_{19}$H$_{20}$N$_2$O$_3$ (M+1) requires 325.1552]; Major isomer: $^1$H NMR (400 MHz, CDCl$_3$): 8.14 (2 H, d, $J = 8.8$, ArH), 7.56 (2 H, m, ArH), 7.07 (2 H, t, $J = 7.9$, ArH), 6.66 (1 H, dd, $J_1 = 13.2$, $J_2 = 6.9$, ArH), 6.49 (2 H, d, $J = 7.7$, ArH), 4.86 (0.47 H, d, $J = 4.5$, syn-CH), 4.71 (0.53 H, d, $J = 5.3$, anti-CH), 4.86 (0.47 H, br, syn-NH), 4.60 (0.47 H, br, anti-NH), 2.85 (1 H, dd, $J_1 = 11.0$, $J_2 = 5.0$, CH), 2.37 (2 H, dt, $J_1 = 26.2$, $J_2 = 13.9$, CH$_2$), 2.00 (3 H, m, CH$_2$), 1.70 (3 H, m, CH$_2$). $^{13}$C NMR (101 MHz, CDCl$_3$): 211.74, 210.60, 149.89, 149.61, 147.08, 147.03, 146.71, 146.67, 129.27, 129.17, 128.62, 128.27, 123.66, 123.61, 118.37, 118.10, 114.05, 113.50, 57.77, 57.21, 57.03, 56.21, 42.45, 42.41, 32.01, 29.09, 27.78, 27.05, 24.94, 24.49.
4q

4-phenyl-4-(phenylamino)-2-butanone (4q): Yield, 71%; white solid; mp 90-92 °C; Rf 0.43 (hexane/ethyl acetate = 4:1); IR (KBr): 3369, 1704; HRMS (ESI) m/z 240.1361 [C₁₆H₁₇NO (M+1) requires 240.1388]; ¹H NMR (400 MHz, CDCl₃) 7.26 (m, 4H), 7.16 (d, J = 6.0 Hz, 1H), 7.01 (t, J = 7.8 Hz, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.47 (d, J = 8.1 Hz, 2H), 4.77 (t, J = 6.5 Hz, 1H), 4.36 (s, 1H), 2.84 (d, J = 6.5 Hz, 2H), 2.02 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) 206.1, 145.8, 141.5, 128.1, 127.8, 126.3, 125.2, 116.8, 112.7, 53.3, 50.2, 29.7.

4r

4-(4-chlorophenyl)-4-(phenylamino)-2-butanone (4r). Yield, 68%; yellow solid; mp 122-124 °C; Rf 0.40 (hexane/ethyl acetate = 4:1); IR (KBr): 3367, 1706; HRMS (ESI) m/z 274.0908 [C₁₆H₁₅NOCl (M+1) requires 274.0920]; ¹H NMR (400 MHz, CDCl₃): δ 7.22 (m, 4H), 7.04 (t, J = 7.7 Hz, 2H), 6.62 (t, J = 7.2 Hz, 1H), 6.45 (d, J = 8.0 Hz, 2H), 4.75 (t, J = 6.3 Hz, 1H), 4.38 (s, 1H), 2.85 (d, J = 6.3 Hz, 2H), 2.05 (s, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 206.7, 146.5, 141.1, 133.0, 129.2, 127.7, 118.1, 113.8, 53.8, 51.0, 30.8.

4s

4-(4-methoxyphenyl)-4-(phenylamino)-2-butanone (4s): Yield, 79%; yellow solid; mp 104-105 °C; Rf 0.44 (hexane/ethyl acetate = 4:1); IR (KBr): 3363, 1707; HRMS (ESI) m/z 270.1461 [C₁₇H₁₉NO₂ (M+1) requires 269.1416]; ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, J = 7.0 Hz, 2H), 7.09 (t, J = 7.0 Hz, 2H), 6.85 (d, J = 6.9 Hz, 2H), 6.66 (t, J = 7.3 Hz, 1H), 6.54 (d, J = 7.7 Hz, 2H), 4.80 (t, J = 6.3 Hz, 1H), 3.78 (s, 3H).
4.38 (s, 1H), 3.77 (s, 3H), 2.90 (d, $J = 6.5$ Hz, 2H), 2.08 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): δ 207.3, 158.8, 146.8, 134.4, 129.1, 127.4, 117.8, 114.2, 113.8, 55.2, 53.8, 51.3, 30.8.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 207.3, 158.8, 146.8, 134.4, 129.1, 127.4, 117.8, 114.2, 113.8, 55.2, 53.8, 51.3, 30.8.

2-Methyl-1-Phenyl-1-(N-phenylamino)pentan-3-one (4t): Yield, 85%; white solid; mp 105-106 °C; Rf 0.40 (hexane/ethyl acetate = 4:1); IR (KBr): 3407, 3370, 1708; HRMS (ESI) $m/z$ 268.1699 [C$_{18}$H$_{21}$NO (M+1) requires 268.1701]; Major isomer: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.20-7.26 (m, 5H), 7.02 (t, $J = 5.9$ Hz, 2H), 6.59 (s, 1H), 6.45 (d, $J = 5.6$ Hz, 2H), 4.62 (s, 1H), 4.29 (s, 1H, NH), 2.96 (s, 1H), 2.27-2.30 (m, 2H), 1.05-1.07 (m, 3H), 0.89 (td, $J = 7.2$, 4.0 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 213.30, 147.03, 141.22, 129.06, 128.59, 127.27, 126.85, 117.66, 113.65, 59.24, 52.25, 35.52, 11.57, 7.50.

2-Methyl-1-Phenyl-1-[N-(4-Methoxyphenylamino) pentan-3-one (4u): Yield, 91%; white solid; Rf 0.53 (hexane/ethyl acetate = 4:1); IR (KBr): 3365, 1703; HRMS (ESI) $m/z$ 298.1802 [C$_{19}$H$_{23}$NO$_2$ (M+1) requires 298.1807]; Major isomer: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (d, $J = 4.4$ Hz, 4H), 7.22 (dt, $J = 8.6$, 4.2 Hz, 1H), 6.66 (d, $J = 8.9$ Hz, 2H), 6.45 (d, $J = 8.9$ Hz, 2H), 4.59 (d, $J = 5.7$ Hz, 1H), 3.68 (s, 3H), 2.98 (dd, $J = 6.8$, 6.0 Hz, 1H), 2.35 (dd, $J = 12.6$, 7.2 Hz, 2H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 212.45, 151.15, 140.48, 140.24, 127.54, 126.19, 125.89, 113.87, 113.70, 59.03, 54.67, 51.30, 34.49, 10.49, 6.50.
**2-Methyl-1-Phenyl-1-[N-(4-Chlorophenylamino)]pentan-3-one (4v):** Yield, 82%; yellowish solid; mp 112-114 °C; Rf 0.32 (hexane/ethyl acetate = 4:1); IR (KBr): 3376, 1715; HRMS (ESI) m/z 306.1309 [C₁₈H₂₀ClNO (M+1) requires 306.1312]; Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.17 (m, 5H), 7.06 – 6.92 (m, 2H), 6.47 – 6.30 (m, 2H), 4.59 (d, J = 5.0 Hz, 1H), 4.41 (s, 1H), 2.99 (dd, J = 6.9, 5.8 Hz, 1H), 2.32 (ddd, J = 14.3, 8.9, 5.3 Hz, 2H), 1.10 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 213.31, 145.59, 140.66, 128.89, 128.68, 127.46, 126.81, 114.78, 59.38, 52.04, 35.55, 11.58, 7.48.

**2-Methyl-1-(4-Chlorophenyl)-1-(N-phenylamino) pentan-3-one (4w):** Yield, 81%; yellowish solid; Rf 0.39 (hexane/ethyl acetate = 4:1); IR (KBr): 3376, 1692; HRMS (ESI) m/z 306.1307 [C₁₈H₂₀ClNO (M+1) requires 306.1312]; Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.17 (t, J = 8.2 Hz, 4H), 6.99 (t, J = 7.5 Hz, 2H), 6.57 (d, J = 7.1 Hz, 1H), 6.38 (d, J = 7.5 Hz, 2H), 4.56 (d, J = 5.3 Hz, 1H), 2.87-2.90 (m, 1H), 2.24-2.31 (m, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 211.97, 145.69, 138.85, 131.93, 128.09, 127.76, 127.27, 116.92, 112.66, 57.63, 50.98, 34.55, 10.56, 6.48.
2-Methyl-1-(4-methoxyphenyl)-1-[N-(4-Chlorophenylamino)] pentan-3-one (4x): Yield, 83%; yellowish solid; Rf 0.48 (hexane/ethyl acetate = 4:1); IR (KBr): 3365, 1720; HRMS (ESI) m/z 332.1415 [C_{19}H_{22}ClNO (M+1) requires 332.1417]; Major isomer: ^1H NMR (400 MHz, CDCl₃) δ 7.09 (t, J = 10.7 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.76 (dd, J = 8.5, 4.9 Hz, 2H), 6.34 (t, J = 6.0 Hz, 2H), 4.47 (s, 1H), 4.31 (s, 1H), 3.70 (d, J = 3.5 Hz, 3H), 2.98 – 2.82 (m, 1H), 2.36 – 2.12 (m, 2H), 1.03 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^13C NMR (101 MHz, CDCl₃) δ 212.46, 157.71, 146.08, 132.13, 128.01, 126.87, 116.54, 112.95, 112.63, 57.73, 54.18, 51.38, 34.58, 10.79, 6.48

![Structure of 2-Methyl-1-(4-methoxyphenyl)-1-[N-(4-Chlorophenylamino)] pentan-3-one (4x)](image)

1-phenyl-1-(phenylamino)-3-hexanone (4y): Yield, 77%; white solid; mp 87-88 °C; Rf 0.51 (hexane/ethyl acetate = 4:1); IR (KBr): 3376, 1703; HRMS (ESI) m/z 268.1692 [C_{18}H_{21}NO (M+1) requires 268.1701]; δ ^1H (400 MHz, CDCl₃) 7.29 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 5.8 Hz, 1H), 7.02 (t, J = 7.6 Hz, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 7.8 Hz, 2H), 4.78 (t, J = 6.4 Hz, 1H), 4.48 (s, 1H), 2.82 (d, J = 6.4 Hz, 2H), 2.28 - 2.17 (m, 2H), 1.51 - 1.41 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H); δ ^13C (101 MHz, CDCl₃) 208.4, 145.8, 141.6, 128.1, 127.7, 126.3, 125.3, 116.7, 112.7, 53.4, 49.2, 44.6, 15.8, 12.5.
6. ESI mass spectra

Figure S2: ESI(+)‐MS for CID of Cp₂TiCl₂ in CH₃OH solution (m/z 100‐450).
Figure S3: ESI(+)-MS for CID of Cp₂TiCl₂ in CH₃OH (m/z 206-213).
Figure S4: ESI(+)−MS for CID of Cp₂TiCl₂ in CH₃OH(m/z 237-244).
7. Copies of $^1$H NMR and $^{13}$C NMR spectra