Hydrophobically-Directed Selective Reduction of Ketones

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Supporting Information

I. General Information:

a. Chemicals: THF, CH₂Cl₂, DMF, and ether were dried through columns of activated molecular sieves. Other solvents, inorganic salts, and organic reagents were purchased from commercial sources and used without further purification unless otherwise mentioned.

b. Chromatography: Merck pre-coated 0.25 mm silica plates containing a 254 nm fluorescence indicator were used for analytical thin-layer chromatography. Flash chromatography was performed on 230-400 mesh silica (Silica Gel 60) from EM Science.

c. Spectroscopy: NMR spectra were obtained on a Bruker DPX 300 or 400 MHz spectrometer. APCI MS spectra were taken on a Nermag R-10-10 instrument. FAB MS spectra were taken on a JEOL JMS-DX-303 HF instrument using either glycerol or p-nitrobenzyl alcohol as matrices. All data processing was performed using Bruker XMass/XTOF V 5.0.2.

II. General Procedure for Competition Reactons:

3-Ketopropionic Acid Series:

0.6 mmol **2a** and **3** (free acids) were added to 4 ml 1.0M Na₂CO₃/D₂O. After stirring, solution was homogeneous. 0.03 mmol of appropriate substituted lithium borohydride was added. After having stirred for 20 minutes, ¹H NMR (400 Mhz) analysis was performed. Ratio of signal from hydrogens from reduction of **2a** and **3** was used to determine ratio of reduction products.

Quaternized □-Keto amine Series:

0.08 mmol **6a** and **7** was added to 4 ml D₂O. 2 mg NaHCO₃ was added to facilitate exchange of □-keto protons next to quaternized amine. Protons of acetyl group are not rapidly exchanged under these conditions. After stirring for 5 minutes, approximately 0.005 mmol of appropriate substituted lithium borohydride was added. Ratio of signal from hydrogens from reduction of **6a** and **7** was used to determine ratio of reduction products.

III. Synthesis:

Trimethyl-(2-oxo-2-methyl-ethyl)ammonium triflate (7):

Dimethylaminoacetone (0.2 g, 0.0020 mol) was added to 40 ml dry CH₂Cl₂. Methyl triflate (0.38g, (0.0023 mol) was then added dropwise at room temperature. The mixture was allowed to

stir for 30 minutes. TLC (90:10 CH₂Cl₂:MeOH) showed no remaining dimethylaminoacetone. An orange oil was precipitated upon addition of 200 ml hexanes. The orange oil solidifies into an orange-yellow solid when dried on high-vac. The isolated yield was 0.44 g (83%). ¹H NMR (400 Mhz, DMSO-d₆): δ 4.53 (s, 2H), 3.16 (s, 9H), 2.14 (s, 2H). ¹H NMR (400 Mhz, D₂O): δ 4.42 (s, 2H), 3.17 (s, 9H), 2.13 (s, 3H). ¹³C NMR (100 Mhz, DMSO-d₆): δ 199.8, 69.0, 53.0, 28.4. FAB+ MS: 381.2 (2M⁻OTf), 116.1 (M⁻OTf).

Trimethyl-(2-oxo-2-phenyl-ethyl)ammonium triflate (6a):

2-Bromoacetophenone (2 g, 0.010 mol) was added to 100 ml dry THF. 2M Me₂NH in THF (45 ml, 0.090 mol) was added to the reaction mixture. Solution becomes cloudy upon addition. After stirring at room temperature for 45 minutes, all 2-Bromoacetophenone was gone by TLC (80:20 Hexane:EtOAc). 100 ml aqueous NaHCO₃ was added. The solution was extracted twice with ether. Combined ether layers were washed with brine and dried over MgSO₄. After rotovap, a yellow-orange liquid remained. This liquid was dissolved into 100 ml CH₂Cl₂. Methyl triflate (2.2 g, 0.013 mol) was added dropwise at room temperature. White solid immediately crashed out. Solution was filtered after stirring for 30 minutes. 1.96 g (60% for two steps) of a white solid was isolated. ¹H NMR (400 Mhz, DMSO-d₆): δ 7.98 (d, 2H, J=7.5 Hz), 7.75 (t, 1H, J=7.4 Hz), 7.62 (t, 2H, J=7.7 Hz), 5.26 (s, 2H), 3.30 (s, 9H). ¹³C NMR (100 Mhz, DMSO-d₆): δ 190.8, 134.4, 134.0, 128.7, 127.6, 67.1, 53.4. FAB+ MS: 505.2 (2M⁻OTf), 178.2 (M⁻OTf).

Trimethyl-(2-oxo-2-naphthyl-ethyl)ammonium triflate (6b):

Procedure for the preparation of **6a** followed using 2-Bromoacetophenone instead of 2-Bromoacetophenone. An off-white solid was isolated in a yield of 54% for the two steps. ¹H NMR (400 Mhz, DMSO-d₆): δ 8.71 (s, 1H), 8.16 (d, 1H, J=8.2 Hz), 8.12 (d, 1H, J=8.6 Hz), 8.06 (d, 1H, J=8.0 Hz), 8.00 (d, 1H, J=8.6 Hz), 7.75 (t, 1H, J=7.8 Hz), 7.69 (t, 1H, J=8.0 Hz), 5.41 (s, 2H), 3.36 (s, 9H). ¹³C NMR (100 Mhz, DMSO-d₆): δ 190.2, 135.2, 131.5, 131.3, 130.0, 129.3, 129.2, 128.4, 127.6, 127.2, 122.6, 67.2, 53.5. FAB+ MS: 605.2 (2M⁻OTf), 228.2 (M⁻OTf).

Lithium Pentafluorophenylborohydride:

Pentafluorophenylboronic acid (1 g, 0.0047 mol) was added to 70 ml dry ether in a flame-dried 100 ml Schlenk flask. 1M LiAlH₄ in ether (8 ml, 0.0080 mol) was added dropwise under argon. Solution stirred at room temperature for 40 minutes. The excess LiAlH₄ was carefully quenched with 1ml H₂O. The ether was removed on a high vac and 100 ml distilled H₂O was added. After stirring for 20 minutes, the solution was filtered through a fritted filter. Collected filtrate was clear. The filtrate was frozen and rotovapped. A gel-like cloudy solid remained. 80 ml ether was added. White solid formed and was filtered. Ether was rotovapped and remaining material was dissolved in an additional 40 ml ether. Small amount of white solid that formed was again filtered. Ether was removed on a high-vac. 25 ml benzene was added, frozen, and placed on high vac. 0.25g (28%) of a white powder remained. ¹H NMR (300 Mhz, D₂O): δ 0.70-1.53 (quartet J=82.5 Hz of triplets J=5.7 Hz). ¹¹B NMR (96.2 Mhz, D₂O): δ -36 (q, J=87 Hz). ¹⁹F NMR (282 Mhz, D₂O): 37.2 (t, 1F, J = 20.0 Hz), 35.0 (m, 2F), -131.9 (m, 2F).

Lithium Naphthylborohydride:

2-Naphthylboronic acid (1.0 g, 0.0058 mol) was added to 250 ml dry ether in a flame-dried Schlenk flask. 1M LiAlH₄ in ether (10 ml, 0.01 mol) was added dropwise under argon. The reaction mixture was allowed to stir overnight. The ether was removed on a high vac and 100 ml dry pentane was added. After stirring for 10 minutes, the cloudy supernatant liquid was transferred to another flask via filtered syringe. An additional 100 ml pentane was added to the reaction flask and the extraction procedure was repeated. Pentane was removed on a high vac and 100 ml benzene was added to the wet white solid that remained. The benzene solution was frozen and placed on a high vac until all benzene was removed. 0.36 g (42%) of a white solid was isolated. ¹H NMR indicated that the lithium naphthylborohydride was contaminated with 2-Naphthylboronic acid. ¹H NMR (400 Mhz, THF-d₈): δ 7.57 (s, 1H), 7.40 (m, 3H), 7.25 (d, 1H, J=8.2 Hz), 7.03 (t, 1H, J=7.3 Hz), 6.96 (t, 1H, J=7.2 Hz), 1.15 (q, 3H, J=77.7 Hz). ¹¹B NMR (96.2 Mhz, THF-d₈): δ -26.8 (q, 79 Hz).

Synthesis of 10a, 10b, and 10c:

1-[Methyl-(2-methylamino-ethyl)-amino]-propan-2-ol:

N, N'-dimethyl-1,3-propanediamine (13.5 g, 0.13 mol) was added to 50 ml MeOH. Propylene oxide (3 ml, 0.04 mol), was added via syringe. Solution was stirred for 3 hours at room temperature. MeOH was removed on rotovap. Product was distilled under high vac (0.5 torr) from 72-76°C. 4.2 g of a colorless liquid was isolated (66% based upon added propylene oxide). ¹H NMR (300 Mhz, CDCl₃): δ 3.80 (m, 1H), 2.62 (t, 2H, J=7 Hz), 2.55 (t, 1H, J=7 Hz), 2.41 (s, 3H), 2.36 (m, 1H), 2.25 (s, 3H), 2.25 (m, 2H), 1.64 (p, 2H, J=7 Hz), 1.11 (d, 3H, J=6 Hz). ¹³C NMR (100 Mhz, CDCl₃): δ 65.5, 63.2, 55.4, 50.0, 42.4, 36.5, 27.4, 20.1. APCI+ MS: 161.1 (M+1)

1-(Methyl-{3-[methyl-(2-oxo-2-phenyl-ethyl)-amino]-propyl}-amino)-propan-2-one:

1-[Methyl-(2-methylamino-ethyl)-amino]-propan-2-ol (1.2 g, 0.0075 mol) was added to 60 ml dry THF. Cs₂CO₃ was added (2.4 g, 0.0075 mol) followed by 2-Bromoacetophenone (1.34 g, 0.0068 mol) dissolved in 10 ml THF. The reaction mixture was stirred overnight at room temperature. TLC showed no remaining 2-Bromoacetophenone (20:1 CH₂Cl₂:MeOH). 100 ml H₂O was added. The solution was extracted three times with ether. Combined ether layers were washed with brine and dried over MgSO₄. After rotovap, a viscous orange liquid remained. 75 ml acetone and 8 ml H₂O were added. While stirring, 3 ml H₂SO₄ was added. After the reaction mixture cooled to room temperature, 4 ml Jones' Reagent was added (Jones' Reagent was prepared by adding 16 g CrO₃ to 56 ml H₂O, to which 16 ml H₂SO₄ was then added). The solution was initially red. After stirring overnight at room temperature, the solution was green. 150 ml H₂O was added. NaHSO₃ was added until the solution turned blue. The mixture was then extracted twice with ether, which was discarded. Na₂CO₃ was then added until the aqueous layer was powder blue. The aqueous layer was extracted twice with CH₂Cl₂. The combined CH₂Cl₂ layers were washed with brine and dried over MgSO₄. After rotovap, 1.06 g (48% for two steps) of a yellow-orange liquid was isolated. ¹H NMR (300 Mhz, CDCl₃): δ 7.97 (d, 2H, J=7.2 Hz), 7.54 (t, 1H, J=7.4 Hz), 7.43 (t, 2H, J=7.7 Hz), 3.81 (s, 2H), 3.14 (s, 2H), 2.55 (t, 2H, J=7.2 Hz), 2.42 (t, 2H, J=7.2 Hz), 2.36 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H), 1.70 (p, 2H, J=7.5 Hz). APCI+ MS: 275.0 (M-1)⁺

1-(Methyl-{3-[methyl-(2-oxo-2-naphthyl-ethyl)-amino]-propyl}-amino)-propan-2-one:

The procedure for the synthesis of 1-(Methyl-{3-[methyl-(2-oxo-2-phenyl-ethyl)-amino]-propyl}-amino)-propan-2-one was followed. A viscous orange liquid was isolated in a yield of 45% for the two steps. ^1H NMR (300 Mhz, CDCl_3): δ 8.54 (s, 1H), 8.01 (dd, 1H, $J=8.6$ Hz, $J=1.6$ Hz), 7.94 (d, 1H, $J=7.8$ Hz), 7.86 (m, 2H), 7.56 (pd, 2H, $J=7.2$ Hz, $J=1.4$ Hz), 3.97 (s, 2H), 3.16 (s, 2H), 2.62 (t, 2H, $J=7.0$ Hz), 2.45 (t, 2H, $J=7.1$ Hz), 2.42 (s, 3H), 2.25 (s, 3H), 2.11 (s, 3H), 1.74 (p, 2H, $J=7.4$ Hz). APCI+ MS: 325.2 ($\text{M}-1$) $^+$

1-(Methyl-{3-[methyl-(2-oxo-2-biphenyl-ethyl)-amino]-propyl}-amino)-propan-2-one:

The procedure for the synthesis of 1-(Methyl-{3-[methyl-(2-oxo-2-phenyl-ethyl)-amino]-propyl}-amino)-propan-2-one was followed. A viscous red-orange liquid was isolated in a 50% yield for the two steps. ^1H NMR (300 Mhz, CDCl_3): δ 8.05 (d, 2H, $J=8.4$ Hz), 7.65 (d, 2H, $J=8.4$ Hz), 7.60 (d, 2H, $J=7.9$ Hz), 7.45 (t, 2H, $J=7.5$ Hz), 7.38 (t, 1H, $J=7.2$ Hz), 3.83 (s, 2H), 3.15 (s, 2H), 2.56 (t, 2H, $J=7.2$ Hz), 2.43 (t, 2H, $J=7.2$ Hz), 2.38 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H), 1.72 (p, 2H, $J=7.6$ Hz). FAB+ MS: 353.1 ($\text{M}+1$).

Diamino salt 10a:

1-(Methyl-{3-[methyl-(2-oxo-2-phenyl-ethyl)-amino]-propyl}-amino)-propan-2-one (0.42 g, 0.0015 mol) was added to 35 ml CH_2Cl_2 . Methyl triflate (0.59 g, 0.0036 mol) was added. Solution was stirred overnight. In the morning, droplets of orange oil had precipitated. 50 ml hexane was added and more oil precipitated out. The mother liquor was decanted from the oil and the oil was washed with CH_2Cl_2 . After sitting for a few hours, more red oil precipitates out of the mother liquor. This oil was washed with CH_2Cl_2 . 0.59 g (65%) red oil was isolated. When the oil was placed under high vac, it became a fluffy, very hygroscopic, yellow solid. ^1H NMR (300 Mhz, D_2O): δ 8.01 (d, 2H, $J=8.3$ Hz), 7.80 (t, 1H, $J=7.3$ Hz), 7.64 (t, 2H, $J=7.7$ Hz), 5.26 (s, 1H), 4.59 (s, 1H), 3.83 (t, 2H, $J=8.3$ Hz), 3.69 (t, 2H, $J=8.3$ Hz), 3.46 (s, 6H), 3.31 (s, 6H), 2.37 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (100 Mhz, $\text{DMSO}-d_6$): δ 199.5, 190.4, 134.5, 134.0, 128.7, 127.8, 67.4, 65.4, 60.9, 60.6, 51.6, 51.1, 28.6, 16.5. FAB+ MS: 454.6 ($\text{M}-\text{OTf}$).

Diamino salt 10b:

The procedure for the synthesis of 10a was followed. An orange-yellow solid was isolated in a yield of 61%. ^1H NMR (400 Mhz, D_2O): δ 8.51 (s, 1H), 8.01 (d, 1H, $J=8.1$ Hz), 7.96 (d, 1H, $J=8.8$ Hz), 7.92 (d, 1H, $J=8.2$ Hz), 7.88 (dd, 1H, $J=8.8$ Hz, $J=1.6$ Hz), 7.64 (t, 1H, $J=7.1$ Hz), 7.59 (t, 1H, $J=8.0$ Hz), 5.25 (s, 2H), 4.45 (s, 2H), 3.73 (t, 2H, $J=8.3$ Hz), 3.57 (t, 2H, $J=8.4$ Hz), 3.36 (s, 6H), 3.17 (s, 6H), 2.24 (m, 2H), 2.06 (s, 3H). ^{13}C NMR (100 Mhz, DMSO-d_6): δ 199.5, 190.3, 135.3, 131.5, 131.4, 130.1, 129.3, 129.2, 128.4, 127.6, 127.3, 122.7, 67.3, 65.5, 60.8, 60.6, 51.7, 51.1, 28.5, 16.5. FAB+ MS: 505.2 (M^+-OTf).

Diamino salt 10c:

The procedure for the synthesis of 10a was followed. A yellow solid was isolated in a yield of 53%. ^1H NMR (400 Mhz, D_2O): δ 7.97 (d, 2H, $J=8.4$ Hz), 7.78 (d, 2H, $J=8.3$ Hz), 7.67 (d, 2H, $J=7.4$ Hz), 7.45 (t, 2H, $J=7.0$ Hz), 7.40 (t, 1H, $J=7.2$ Hz), 5.15 (s, 2H), 4.46 (s, 2H), 3.70 (t, 2H, $J=8.2$ Hz), 3.56 (t, 2H, $J=7.8$ Hz), 3.32 (s, 6H), 3.16 (s, 6H), 2.22 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (100 Mhz, DMSO-d_6): δ 200.7, 191.2, 146.8, 139.1, 133.9, 130.0, 129.6, 127.9, 127.8, 68.5, 66.5, 62.0, 61.7, 52.7, 52.2, 29.7, 17.6. FAB+ MS: 530.5 (M^+-OTf).

¹H NMR of **6a**

¹³C NMR of **6a**

FAB+ MS of **6a**

¹H NMR of **6b**

¹³C NMR of **6b**

FAB+ MS of **6b**

¹H NMR of 7

¹³C NMR of 7

FAB+ MS of 7

^1H NMR of **12a**

^{13}C NMR of **12a**

FAB+ MS of **12a**

¹H NMR of **12c**

¹³C NMR of **12c**

FAB+ MS of **12c**

^1H NMR of $\text{LiC}_6\text{F}_5\text{BH}_3$

^{11}B NMR of $\text{LiC}_6\text{F}_5\text{BH}_3$

^{19}F NMR of $\text{LiC}_6\text{F}_5\text{BH}_3$