Supporting Information

Prototype Pictet-Spengler Reactions Catalyzed by Superacids. Involvement of Dicationic Superelectrophiles

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Spectroscopic data of the starting imines and the cyclized products are as follows.

General Methods All melting points were measured with a Yanagimoto hot stage melting point apparatus (MP-500) and are uncorrected. ^{1}H-NMR spectra were measured on a JEOL GX-400 MHz NMR spectrometer with tetramethylsilane and the midpoint of dimethyl sulfoxide (DMSO)-d_6 (2.50 ppm) as an internal reference in $CDCl_3$ at 23 °C and in DMSO-d_6 at 30 °C, respectively, or with CH_2Cl_2 (5.30 ppm) as an internal reference in acid solutions. High-resolution mass spectra (HRMS) were taken with a JEOL JMS-SX102A spectrometer. IR spectra were measured on a Shimadzu IR-408 for a suspension with KBr powder. Flash column chromatography was performed on silica gel (Kieselgel 60, 230-400 mesh, Merck) or aluminum oxide (Aluminum oxide 90, Merck) with a specified solvent. The combustion analyses were carried out in the microanalytical center of this Faculty.

Preparation of *N*-Methylidene-2-phenethylamine 1a To a stirred mixture of 2-phenethylamine (3.04 g, 25 mmol) and $MgSO_4$ (6.04 g) in dry CH_2Cl_2 (30 mL) was added paraformaldehyde (3.83 g, 0.13 mol), and the whole was stirred at room temperature for 2.7 hr. The insoluble materials were removed by suction filtration, and the filtrate was concentrated under reduced pressure to give **1a**. The obtained imine **1a** was pure enough to use without further purification (no signals due to the starting material were detected in the

^{1}H-NMR spectrum). An analytical sample was obtained by recrystallization from n-hexane, mp 36-37 °C. Anal. Calcd for $C_9H_{11}N$: C, 81.16; H, 8.33; N, 10.58. Found: C, 81.10; H, 8.30; N, 10.59. HRMS (M+): Calcd for $C_9H_{11}N$: 133.0891, Found: 133.0884. ^{1}H-NMR ($CDCl_3$): 7.29-7.26 (2H, m), 7.21-7.18 (3H, m), 3.5-3.4 (2H, br s), 2.78-2.68 (4H, m).

Preparation of *N*-(2-Methylpropylidene)-2-phenethylamine 1b The imine **1b** was prepared as described.[17] **1b**: colorless liquid, bp 107 °C / 13.5 mmHg. ^{1}H-NMR ($CDCl_3$): 7.33 (1H, dt, J=5.0, 1.1 Hz), 7.29-7.25 (2H, m), 7.20-7.16 (3H, m), 3.60 (2H, t, J=7.3 Hz), 2.90 (2H, t, J=7.3 Hz), 2.41-2.33 (1H, m), 1.00 (6H, d, J=6.7 Hz). HRMS (M+): Calcd for $C_{12}H_{17}N$: 175.1361, Found: 175.1363.

Preparation of *N*-Benzylidene-2-phenethylamine 1c To a solution of phenethylamine (4.85 g, 40 mmol) in dry EtOH (20 ml) was added benzaldehyde (4.24 g, 40 mmol), and the mixture was heated at reflux for 2 h. The EtOH was evaporated, and the residue was distilled under reduced pressure (bp 147 °C / 5 mmHg) to give the residue, which solidified to afford pale yellow crystals after distillation (**1c**, 7.38 g, 91%). **1c**: colorless crystals (recrystallized from n-hexane); mp 34-35 °C (lit[17] 38-39 °C). ^{1}H-NMR ($CDCl_3$): 8.17 (1H, s), 7.72-7.69 (2H, m), 7.43-7.39 (3H, m), 7.30-7.18 (5H, m), 3.87 (2H, td, J=7.7, 1.3 Hz), 3.02 (2H, t, J=7.5Hz). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.02; H, 7.24; N, 6.58.

Preparation of *N*-(4-Chlorobenzylidene)-2-phenethylamine 1d The imine **1d** was prepared as reported.[17] **1d**: colorless plates, mp 42.5-43.0 °C (recrystallized from EtOH, lit [15] 45-45.5 °C). ^{1}H-NMR ($CDCl_3$): 8.11 (1H, s), 7.63 (2H, dt, J=8.4, 2.2 Hz), 7.37 (2H, dt, J=8.4, 2.2 Hz), 7.30-7.26 (2H, m), 7.23-7.18 (3H, m), 3.85 (2H, td, J=7.5, 1.1 Hz), 3.01 (2H, t, J=7.5 Hz). Anal. Calcd for $C_{15}H_{14}NCl$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.75; H, 5.68; N, 5.48.

Preparation of *N*-(4-Methylbenzylidene)-2-phenethylamine 1e The imine **1e** was prepared in a similar manner to **1c**. The crude **1e** was recrystallized from n-hexane, followed by distillation (bp 113-114 °C / 0.06mmHg) to give pure **1e** as colorless crystals,

mp 40-41 °C (lit[17] 42 °C). HRMS (M^+): Calcd for $C_{16}H_{17}N$: 223.1361, Found: 223.1350s. ^{1}H-NMR ($CDCl_3$): 8.13 (1H, br s), 7.59 (2H, d, J=8.3 Hz), 7.30-7.17 (7H, m), 3.84 (2H, td, J=7.5, 1.1 Hz), 3.00 (2H, t, J=7.5 Hz), 2.38 (3H, s). Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.86; H, 7.47; N, 6.34.

Preparation of *N*-Benzylidene-2-(3-Methylphenyl)ethylamine 1f

To a solution of benzaldehyde (4.32 g) in ethanol (15 mL) a solution of 2-(3-methylphenyl)ethylamine (5.50g)[32] in ethanol (10 mL) was added. The whole was refluxed for 1.5 hr, followed by evaporation of ethanol. The residue was distilled under reduced pressure to give 7.71 g (85%) of the imine **1f** (bp. 149 °C/3 mmHg) as a colorless liquid. ^{1}H-NMR ($CDCl_3$): 8.18 (1H, br s), 7.72-7.69 (2H, m), 7.43-7.39 (3H, m), 7.17 (1H, t, J=7.5 Hz), 7.05-7.00 (3H, m), 3.85 (2H, td, J=7.7 Hz, 1.3 Hz), 2.97 (2H, t, J=7.7 Hz), 2.32 (3H, s).

Preparation of *N*-Benzylidene-2-(3,5-dimethylphenyl)ethylamine 1g

The imine **1g** was prepared from benzaldehyde and 2-(3,5-dimethylphenyl)-ethylamine[33] in ethanol in a similar manner to **1f**. **1g**: colorless liquid, bp. 157-158 °C/ 3 mmHg. HRMS (M^+): Calcd for $C_{17}H_{19}N$: 237.1517, Found: 237.1505. ^{1}H-NMR ($CDCl_3$): 8.20 (1H, br s), 7.73-7.69 (2H, m), 7.43-7.38 (3H, m), 6.86 (2H, s, br), 6.84 (1H, br s), 3.83 (2H, td, J=7.7 Hz, 1.3 Hz), 2.93 (2H, t, J=7.7 Hz), 2.28 (6H, d, J=0.6 Hz).

Preparation of *N*-Benzylidene-2-(3,5-dimethoxylphenyl)ethylamine 1h

The imine **1h** was prepared from benzaldehyde and 3,4-dimethoxyphenethylamine in ethanol in a similar manner to **1f**. **1h**: bp. 180-182 °C/ 8 mmHg. HRMS (M^+): Calcd for $C_{17}H_{19}NO_2$: 269.1416, Found: 269.1416. ^{1}H-NMR ($CDCl_3$): 8.12 (1H, s), 7.71-7.69 (2H, m), 7.42-7.39 (3H, m), 6.81-6.74 (3H, m), 3.87-3.83 (5H, m), 3.79 (3H, s), 2.97 (2H, t, J=7.3 Hz).

Acid-Catalyzed Cyclization of *N*-Methylidene-2-phenethylamine 1a to 1,2,3,4-Tetrahydroisoquinoline 2a:

(1) Direct Separation of 2a

2a: oil, ^{1}H-NMR: 7.15-7.07 (3H, m), 7.02-6.98 (1H, m), 4.02 (2H, brs), 3.15 (2H, t, J=6.0 Hz), 2.80 (2H, t, J=6.0 Hz). HRMS (M^+): Calcd for $C_9H_{11}N$: 133.0891, Found: 133.0882. HCl salt of **2a**: mp 201.5-202 °C (recrystallized from ethanol/n-hexane). (lit 197-198 °C)[33] Anal. Calcd for $C_9H_{12}NCl$: C, 63.72; H, 7.13; N, 8.26. Found: C, 63.67; H, 7.04; N, 8.29. ^{1}H-NMR (DMSO-d_6): 9.57 (2H, brs), 7.28-7.20 (4H, m), 4.23 (2H,s), 3.36-3.32 (2H, m), 3.01 (2H, t, J=6.2 Hz). The amine **2a** obtained above was identical with authentic 1,2,3,4-tetrahydroisoquinoline in terms of the ^{1}H-NMR spectrum.

(2) Separation after Benzoylation

TFSA-TFA: *N*-Benzoyl-1,2,3,4-tetrahydroisoquinoline (the *N*-benzoyl form of **2a**): oil, ^{1}H-NMR ($CDCl_3$): two steroisomers (3:2) with respect to the amide configuration: Major: 7.44 (4H, m), 7.21 (5H, m), 4.90 (2H, brs), 3.64 (2H, brs), 2.88 (2H, brs). Minor: 7.44 (6H, m), 7.21 (2H, m), 6.91 (1H, brs), 4.59 (2H, brs), 3.99 (2H, brs), 2.98 (2H, brs). HRMS (M^+): Calcd for $C_{16}H_{13}NO$: 237.1155, Found: 237.1154. *N*-benzoyl-2-phenethylamine: mp 115.5-116 °C (colorless plates, recrystallized from n-hexane). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.88; H, 6.66; N, 6.19. ^{1}H-NMR: 7.69 (2H, d, J=7.3 Hz), 7.48 (1H, t, J=7.3 Hz), 7.40 (2H, t, J=7.7 Hz), 7.33 (2H, t, J=7.7 Hz), 7.25 (3H, m), 3.73 (2H, quartet), 2.94 (2H, t).

1-(1-Methylethyl)-1,2,3,4-tetrahydroisoquinoline (2b): **2b**:^{1}H-NMR ($CDCl_3$): 7.19-7.08 (4H, m), 4.02 (1H, d, J= 3.8 Hz), 3.39-3.32 (1H, m), 3.00-2.87 (2H, m), 2.75-2.68 (1H, m), 2.41-2.33 (1H, m), 1.15 (3H, d, J=7.0 Hz), 0.78 (3H, d, J=7.0 Hz). HRMS (M^+): Calcd for $C_{12}H_{17}N$: 175.1361, Found: 175.1362. Picrate of **2b**: Yellow crystals, mp 145.7-146.3 °C (recrystallized from EtOH, lit 142-142.5 °C)[34]. Anal (picrate). Calcd for $C_{18}H_{20}N_4O_7$: C, 53.46; H, 4.99; N, 13.86. Found: C, 53.52; H, 5.01; N, 13.97.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2c): Colorless needles, mp 97.0-98.0 °C (recrystallized from EtOH / n-hexane, lit 97-98 °C)[34]. Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.79; H, 7.38; N, 6.68. ^{1}H-NMR ($CDCl_3$): 7.35-7.26

(5H, m), 7.15 (2H, d, J=4.0 Hz), 7.07-7.02 (1H, m), 6.75 (1H, d, J=7.7 Hz), 5.11 (1H, s), 3.30-3.24 (1H, m), 3.13-3.01 (2H, m), 2.88-2.81 (1H, m).

1-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (2d): Colorless prisms, mp 80.5-82.5 °C (recrystallized from ethyl acetate / n-hexane). Anal. Calcd for $C_{15}H_{14}NCl$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.91; H, 5.57; N, 5.81. ^{1}H-NMR ($CDCl_3$): 7.29 (2H, td, J=8.4, 2.2 Hz), 7.21 (2H, td, J=8.4, 2.2 Hz), 7.16-7.14 (2H, m), 7.07-7.02 (1H, m), 6.71 (1H, d, J=7.3 Hz), 5.08 (1H, s), 3.28-3.21 (1H, m), 3.13-3.00 (2H, m), 2.87-2.80 (1H, m). HCl salt: Colorless needles, mp 233.0-234.0 °C (recrystallized from HCl-EtOH, lit 233-236 °C)[31]. ^{1}H-NMR (DMSO-d_6): 10.16 (1H, br s), 9.63 (1H, br s), 7.55 (2H, d, J=8.6 Hz), 7.43 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=4.0 Hz), 7.20-7.15 (1H, m), 6.71 (1H, d, J=8.1 Hz), 5.81 (1H, br s), 3.47-3.24 (3H, m), 3.11-3.04 (1H, m).

1-(4-Methylphenyl)-1,2,3,4-tetrahydroisoquinoline (2e): HRMS (M^+): Calcd for $C_{16}H_{17}N$: 223.1361, Found: 223.1349. ^{1}H-NMR ($CDCl_3$): 7.17-7.12 (6H, m), 7.06-7.01 (1H, m), 6.76 (1H, d, J=7.7 Hz), 5.08 (1H, s), 3.30-3.23 (1H, m), 3.12-3.00 (2H, m), 2.87-2.80 (1H, m), 2.34 (3H, s). HCl salt: Colorless needles, mp 290.0-291.0 °C (from EtOH, lit 282-286 °C).[34] ^{1}H-NMR (DMSO-d_6): 10.03 (1H, br s), 9.42 (1H, br s), 7.31-7.27 (6H, m), 7.19-7.15 (1H, m), 6.71 (1H, d, J=7.7 Hz), 5.72 (1H, br s), 3.38-3.24 (3H, m), 3.07 (1H, td, J=7.0, 5.2 Hz), 2.34 (3H, s). Anal., Calcd for $C_{16}H_{18}NCl$: C, 73.98; H, 6.98 N, 5.39. Found: C, 73.87; H, 7.20; N, 5.23.

1-Phenyl-6-methyl- (2f) and 1-Phenyl-8-methyl-1,2,3,4-tetrahydroisoquinoline (2f'): The residue (232.3 mg) obtained in the reaction of **1f** in TFSA at 120 °C was flash-chromatographed (ethyl acetate-methanol 20:1) to give a mixture of **2f** and **2f'** (187.9 mg, 77 % in total). The ratio of the isomers was estimated to be 3:1 (**2f**: **2f'**) by means of ^{1}H-NMR spectroscopy. The residue was fractionally recrystallized from n-hexane to give a single isomer of the major product: 1-phenyl-6-methyl-1,2,3,4-tetrahydroisoquinoline (**2f**): Colorless needles, mp 106.5-107.0 °C. HRMS (M^+): Calcd for $C_{16}H_{17}N$: 223.1361, Found: 223.1366. ^{1}H-NMR ($CDCl_3$): 7.34-7.22 (5H, m), 6.97 (1H,

s), 6.86 (1H, d, 7.7Hz), 6.64 (1H, d, 8.1 Hz), 5.07 (1H, s), 3.27 (1H, td,4.8 Hz, 11.0 Hz), 3.11-2.97 (2H, m), 2.79 (1H, td, 4.8 Hz, 15.4 Hz), 2.30 (3H, s). 1-phenyl-8-methyl-1,2,3,4-tetrahydroisoquinoline (**2f'**): ^{1}H-NMR: 7.31-7.25 (3H, m), 7.13 (1H, t, J=7.7 Hz), 7.09-7.05 (3H,m), 6.95 (1H, m), 5.18 (1H, s), 3.10-2.90 (3H, m), 2.88-2.70 (1H, m), 1.89 (3H, s).

1-Phenyl-6,8-dimethyl-1,2,3,4-tetrahydroisoquinoline (2g): HRMS (M^+): Calcd for $C_{17}H_{19}N$: 237.1517, Found: 237.1522. ^{1}H-NMR ($CDCl_3$): 7.30-7.21 (3H, m), 7.12-7.09 (2H, m), 6.87 (1H, br s), 6.80 (1H, br s), 5.19 (1H, s), 3.01-2.88 (3H, m), 2.81-2.71 (1H, m), 2.30 (2H, s), 1.84 (3H, s). HCl salt: Colorless : mp: 276.5-277.5 °C (recrystallized from n-hexane). Anal., Calcd for $C_{17}H_{20}NCl$: C, 74.57; H, 7.36 N, 5.12. Found: C, 74.47; H, 7.58; N, 5.06. ^{1}H-NMR (DMSO-d_6): 10.23 (1H, br s), 9.39 (1H, br s), 7.42-7.39 (3H, m), 7.25-7.22 (2H, m), 6.99 (1H, s), 6.90 (1H, s), 5.83 (1H, s), 3.24-3.14 (2H, m), 3.05-2.96 (2H, m), 2.27 (3H, s), 1.79 (3H, s).

1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2h): Colorless prisms, mp 133-134 °C (recrystallized from ethanol/n-hexane). Anal., Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11 N, 5.20. Found: C, 75.91; H, 7.35; N, 4.95. ^{1}H-NMR (DMSO-*d6*): 7.35-7.24 (5H, m), 6.63 (1H, s), 6.25 (1H, s), 5.05 (1H, br s), 3.87 (3H, s), 3.64 (3H, s), 3.22 (1H, dt, 12.1 Hz, 5.1 Hz), 3.05 (1H, ddd, 12.1 Hz, 8.2 Hz, 4.6 Hz), 2.97-2.90 (1H, m), 2.75 (1H, dt, 16.1 Hz, 4.9 Hz).