Preparation of N-Aryl Azacrown Ether Derivatives Using Arene-Iron Chemistry
Anthony J. Pearson* and Wenjing Xiao

1. Detailed experimental procedure for 2b-d, 3b-f, 4b-f, 5b, 9b-c and 10b-c.

[(η^5-Cyclopentadienyl)(η^6-(1-(4-hydroxypiperazino)-4-(4,7,10,13-tetraoxa-1-azacyclopentadecyl))benzene)]iron Hexafluorophosphate (3b) To a solution of complex 2a (in one pot with the first step beginning with 200 mg, 0.46 mmol compound 1) in 8 mL CH_3CN was added 4-hydroxypiperazine (8 equiv), the reaction mixture was refluxed under argon overnight, the mixture was filtered through Celite, then was rotary evaporated. The dark red residue was washed with ether (40 mL x 2) to remove excess crown ether and 4-hydroxypiperazine, and the crude product was submitted to demetallation. ^1H NMR (200 MHz, CD_3COCD_3): δ 5.74 (4H, s), 4.95 (5H, s). HRMS – FAB: Calculated for C_{26}H_{36}O_{5}N_{2}Fe 515.2208; Found 515.2201.

1-(4-Hydroxypiperazino)-4-(4,7,10,13-tetraoxa-1-azacyclopentadecyl) benzene (4b) The crude 3b was dissolov in 50 mL CH_3CN, and irradiated with 100 W Q-beam halogen lamp under argon for 3.5 h. The mixture was filtered through Celite, and the solvent was removed by rotary evaporation. The residue was purified by flash chromatography (silica gel, acetone/hexanes/Et_3N: 1/2/0.1, R_f = 0.2), to afford the product as a colorless oil (140 mg, overall yield from 1 is 77%). ^1H NMR (200 MHz, CD_3COCD_3): δ 6.85 (2H, d, J = 9.1), 6.61 (2H, d, J = 9.1), 3.4-3.7 (22H), 3.4 (2H), 2.69 (2H), 1.9 (2H), 1.6 (2H). ^13C NMR (50 MHz, CD_3COCD_3): δ 143.9, 143.3, 120.0, 113.4, 72.0, 71.2, 70.9, 70.8, 69.8, 68.0, 53.4, 50.2, 35.8. HRMS – FAB: Calculated for C_{21}H_{32}O_{5}N_{2} 394.2468; Found 394.2469.

[(η^5-Cyclopentadienyl)(η^6-(1-chloro-4-(4,7,10,13,16-pentaoxa-1-
zacyclopentadecyl))benzene)]iron Hexafluorophosphate (2b) To a round-bottom flask was added compound 1 (205 mg, 0.5 mmol), 1-aza-18-crown-8 (400 mg, 1.5 mmol), 0.2 mL pyridine and 10 mL THF. The resulting mixture was refluxed under argon overnight, then cooled and filtered through Celite. THF was removed by rotary evaporation, and the red-orange residue was washed with ethyl ether (25 mL x 3) to remove most of the excess crown ether. The crude product was used for preparing complex 3c. ^1H NMR (200 MHz, CD_3COCD_3): δ 6.39 (2H, s), 6.03 (2H, s), 5.04 (5H, s). HRMS – FAB: Calculated for C_{23}H_{17}O_{5}NClFe 494.1397; Found 494.1373.

[(η^5-Cyclopentadienyl)(η^6-(1-(4-piperazino)-4-(4,7,10,13,16-pentaoxa-1-
zacyclopentadecyl))benzene)]iron Hexafluorophosphate (3c) To a solution of complex 2b (380 mg, 0.5 mmol) in 20 mL CH_3CN was added piperazine (25 equiv), the reaction was refluxed under argon overnight, and cooled to rt. The mixture was filtered through Celite, then was rotary evaporated. The residue was taken up in acetone, and excess piperazine was filtered off. After removal of acetone, the residue was submitted directly to demetallation. ^1H NMR (200 MHz, CD_3COCD_3): δ 5.71 (4H, s), 4.95 (5H, s). HRMS – FAB: Calculated for C_{27}H_{43}O_{5}N_{3}Fe 544.2474; Found 544.2478.

1-(4-Piperazino)-4-(4,7,10,13,16-pentaoxa-1-azacyclopentadecyl) benzene (4c) The above crude product 3c was dissolved in 50 mL CH_3CN, and irradiated with 100 W Q-beam halogen lamp for 50 min. The mixture was filtered through Celite, and the solvent was removed by rotary evaporation. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH/Et_3N: 100:5/5, R_f = 0.3), to afford 4c as a red oil (143 mg, 77% overall yield from 1). ^1H NMR (200 MHz, CD_3COCD_3): δ 6.84 (2H, d, J = 9.2), 6.67 (2H, d, J = 9.2), 3.4-3.7 (24H), 3.02 (1H, s), 2.91 (8H, s). ^13C NMR (50 MHz, CD_3COCD_3): δ 144.5, 143.6, 119.3, 114.0, 71.7, 71.6, 71.5,
[(η^5-Cyclopentadienyl)(η^6-(1-chloro-4-(4,10,13-tri(oxa-1,7-diazacyclopentadecyl))benzene)]iron Hexafluorophosphate (2c) To a round-bottom flask was added 1 (357 mg, 0.86 mmole) and 1,7-diaza-15-crown-5 (565 mg, 2.6 mmole). The flask was flushed with argon, and pyridine (0.5 mL, 6 mmole) and 10 mL THF were added. The resulting mixture was refluxed overnight, then cooled and filtered through Celite. The solvent was removed, and the residue was washed with ethyl ether (45 mL × 3). The crude product was divided into two portions and was used immediately for preparing compound 5a and complex 3d. 1H NMR (200 MHz, CD3COCD3): δ 6.52 (2H, d, J = 7.2), 6.14 (2H, d, J = 7.2), 5.12 (5H, s). HRMS-FAB Calculated for C21H30O3ClFe 449.1295; Found 449.1290.

[(η^5-Cyclopentadienyl)(η^6-(1-piperidino-4-(4,10,13-tri(oxa-1,7-diazacyclopentadecyl))benzene)]iron Hexafluorophosphate (3d) One portion of the crude product 2c (396 mg, 0.62 mmol) was dissolved in 10 mL THF, piperidine (10 equiv.) was added. The mixture was refluxed overnight, then filtered through Celite. The solvent was removed by rotary evaporation, and the residue was washed with ether (40 mL). Without further purification, the crude 3d was submitted directly to demetallation. 1H NMR (200 MHz, CD3COCD3): δ 5.76 (4H, s), 4.95 (5H, s). HRMS-FAB Calculated for C26H40O3N3Fe 498.2419; Found 498.2392.

1-Piperidino-4-(4,10,13-tri(oxa-1,7-diazacyclopentadecyl))benzene (4d) The above complex 3d (0.62 mmol) was dissolved in 50 mL CH3CN, and irradiated with 100 W Q-beam halogen lamp under argon for 40 min. The solvent was removed by rotary evaporation, the residue was purified by flash chromatography (silica gel, CHCl3/CH3OH/Et3N: 180/1/20, Rf = 0.3), to afford 4d as a pale yellow oil (143mg, 60% overall yield from 1). 1H NMR (200 MHz, CD3COCD3): δ 6.84 (2H, d, J = 9.0), 6.64 (2H, d, J = 9.0), 3.4-3.7 (16H), 2.94 (4H, t, J = 5.4), 2.70 (4H), 2.2 (1H, br), 1.4-1.7 (6H). 13C NMR (50 MHz, CD3COCD3): δ 145.1, 143.6, 119.9, 114.1, 71.9, 71.2, 70.9, 70.4, 70.1, 69.8, 53.9, 53.6, 53.2, 49.7, 49.5, 27.2, 25.2. HRMS-FAB Calculated for C21H39O3N3 (MH+) 378.2756; Found MH+ 378.2756.

Cyclopentadienyl[(η^6-(1-chloro-4-(4,7,13,16-tetra(oxa-1,10-diazacyclocloctadecyl))benzene)]iron Hexafluorophosphate (2d) To a round-bottom flask was added compound 1 (171 mg, 0.4 mmol) and 1,10- diaza-18-crown-6 (286 g, 2.7 mmol, 2.7 equiv), the flask was flushed with argon, then pyridine (1.3 mL, 16 mmol) and 8 mL THF were added. The resulting mixture was stirred for 7 days at rt. 1H NMR showed no SM, the reaction was carried on for preparing 5b directly. 1H NMR (200 MHz, CD3COCD3): δ 6.53 (2H, d, J = 7.2), 6.07 (2H, d, J = 7.2), 5.1 (5H, s). HRMS-FAB Calculated for C23H33O4N3ClFe 493.1556; Found 493.1575.

1-Chloro-4-(4,7,13,16-tetra(oxa-1,10-diazacyclooctadecyl))benzene (5b) Complex 2d (beginning with 0.13 mmol 1) was dissolved in 40 mL CH3CN, and irradiated with 100 W Q-beam halogen lamp for 2 h. The solvent was removed by rotary evaporation. The residue was purified by flash chromatography (silica gel, CH3Cl/MeOH: 10/1, Rf = 0.3), to afford 5b as pale yellow oil (20 mg, 77% overall yield from 1). 1H NMR (300 MHz, CDCl3): δ 7.11 (2H, q, J = 9.2), 6.58 (2H, q, J = 9.2), 3.6 (20H), 2.80 (4H, t, J = 4.8), 2.21 (1H, br, s). 13C NMR (200 MHz, CDCl3) δ 146.6, 129.0, 120.6, 112.8, 70.6, 70.5, 70.5, 68.6, 50.8, 49.4. HRMS-FAB Calculated for C18H30O4N3Cl (MH+) 373.1894; Found MH+ 373.1891.

[(η^5-Cyclopentadienyl)(η^6-(1-piperidino-4-(4,7,13,16-tetra(oxa-1,10-diazacyclocloctadecyl))benzene)]iron Hexafluorophosphate (3e) To the reaction mixture of 2d (beginning with 0.4 mmol 1) was added piperidine (8 equiv.). The mixture was stirred for 2 days, and filtered through Celite. Excess piperidine and CH3CN were removed by rotary evaporation. Without further purification, the crude product was submitted directly to demetallation. 1H NMR (300 MHz, CD3COCD3) δ 5.8 (4H, q, J = 7.6), 5.0 (5H, s). HRMS-FAB Calculated for C28H44O4N3Fe 542.2681; Found 542.2676.
complex 3e was dissolved in 45 mL CH₃CN, and irradiated with 100 W Q-beam halogen lamp under argon for 3 h. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (silica gel, CH₂OH(NH₃)/Et₂O:1/4, Rf = 0.2), to afford 4e as pale yellow oil (114 mg, 65% overall yield from 1).¹H NMR (200 MHz, CD₂COCD₂): δ 6.84, and 6.65 (2H each, d, J = 9.2), 3.45-3.70 (20H), 2.94 (4H, t, J = 5.3), 2.71 (4H, t, J = 4.8), 1.43-1.7 (6H).¹³C NMR (50 MHz, CD₂COCD₂): δ 144.9, 143.7, 120.0, 114.0, 71.5, 71.4, 71.3, 53.3, 52.1, 50.4, 27.2, 25.2. HRMS–FAB Calculated for C₂₃H₄₀O₄N₃ (MH⁺) 422.3019; Found MH⁺ 422.3010.

[(η⁵-Cyclopentadienyl)(η⁶-(1-(4-hydroxypiperidino)-4-(4,7,10,13-tetraoxa-1,10-diazacyclooctadecyl))benzene)iron Hexafluorophosphate (3f) To a solution of complex 2d (beginning with 0.1 mmol 1) in 8 mL CH₃CN was added 4-hydroxypiperidine (95 mg, 9.5 equiv.). The reaction mixture was refluxed overnight, cooled and filtered through Celite, then rotary evaporated. The dark red residue was submitted to demetallation directly.¹H NMR (200 MHz, CDCl₃): δ 5.50 (4H, q), 4.75 (5H, s). HRMS – FAB: Calculated for C₂₈H₄₆O₅N₂Fe 558.2630; Found 558.2620.

1-(4-Hydroxypiperidino)-4-(4,7,10,13-tetraoxa-1,10-diazacyclooctadecyl)benzene (4f) The above crude 3f was dissolved in 50 mL CH₃CN, and irradiated with 100 W Q-beam halogen lamp for 2.5 h. The mixture was filtered through Celite, and rotary evaporated. The residue was purified by flash chromatography (silica gel, Hexanes/CH₂Cl₂/CH₂OH/Et₃N: 60/120/10/10, Rf = 0.3), to afford 4f as a pale red oil (33 mg, 75% overall yield from 1).¹H NMR (300 MHz, CD₂D₆): δ 6.92 (2H, d, J = 9.1), 6.61 (2H, d, J = 9.1), 3.2-3.6 (23H), 2.69 (6H), 2.35 (2H, br), 1.8 (2H), 1.7 (2H).¹³C NMR (50 MHz, CD₂D₆): δ 144.1, 143.3, 119.9, 114.3, 71.1, 70.8, 69.7, 67.7, 52.0, 49.9, 35.5. HRMS – FAB: Calculated for C₂₃H₄₀O₅N₂ (MH⁺) 438.2968; Found MH⁺ 438.2963.

[(η⁵-Cyclopentadienyl)(η⁶-(1-piperazino-4-(4,7,13,16-tetraoxa-1-benzoyl-10-diazacyclooctadecyl))benzene)iron Hexafluorophosphate (9b) The above crude 8b was dissolved in 4 mL CH₃CN, and piperazine (193 mg, 2.3 mmol) was added. The mixture was heated to reflux overnight, then cooled and filtered through Celite. CH₂CN was removed by rotary evaporation, and the residue was washed with ether (40 mL). Without further purification, the dark-red residue was submitted directly to demetallation.¹H NMR (200 MHz, CD₂COCD₂): δ 7.41 (s), 5.70 (4H, br s), 4.95 (5H, s). HRMS–FAB Calculated for C₃₄H₄₉O₅N₄Fe 647.2896; Found 647.2896.

1-Piperazino-4-(4,7,13,16-tetraoxa-1-benzoyl-10-diazacyclooctadecyl)benzene (10b) The above 9b was dissolved in 40 mL CH₂CN, and irradiated by 100 W Q-beam halogen lamp for 1.5 h. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (silica gel, acetone/Et₃N/CH₂OH: 10/1/1, Rf = 0.2), to afford 10b as red orange oil (66 mg, 56% overall yield from 1).¹H NMR (300 MHz, CD₂COCD₂): δ 7.44 (5H, s), 6.88 (2H, d, J = 9.1), 6.70 (2H, d, J = 9.1), 3.58 (25H), 3.02 (8H, s).¹³C NMR (75 MHz, CD₂COCD₂): δ 171.9, 144.1, 143.7, 138.5, 129.7, 129.1, 127.5, 119.3, 113.9, 71.5, 70.0, 52.4, 52.0, 46.4. HRMS–FAB Calculated for C₂₉H₄₀O₅N₄ (MH⁺) 527.3233; Found MH⁺ 527.3233.

[(η⁵-Cyclopentadienyl)(η⁶-(1-piperazino-4-(4,7,13,16-tetraoxa-1-benzyl-10-diazacyclooctadecyl))benzene)iron Hexafluorophosphate (9c) The above crude 8c (0.21 mmol) was dissolved in 4 mL CH₂CN, piperazine (6 equiv) was added, the mixture was heated to reflux overnight, then filtered through Celite. CH₂CN was removed by rotary evaporation, and the residue was washed with ether. Without further purification, the dark-red residue was submitted directly to demetallation.¹H NMR (200 MHz, CD₂COCD₂): δ 5.73 (4H, br s), 4.97 (5H, s). HRMS–FAB Calculated for C₃₄H₄₉O₅N₄Fe 633.31303; Found 633.3099.

1-Piperazino-4-(4,7,13,16-tetraoxa-1-benzyl-10-diazacyclooctadecyl)benzene (10c) The above crude 9c was dissolved in 30 mL CH₂CN, and irradiated with 100 W Q-beam halogen lamp for 30 min. The solvent was removed by rotary evaporation, and the residue was purified
1. H NMR (200 MHz, CD3COCD3): δ 7.30 (5H), 6.84 (2H, d, J = 9.2), 6.68 (2H, d, J = 9.2), 3.5-3.7 (22H), 2.92 (8H, s), 2.82 (1H, br), 2.80 (4H, t, J = 4.9). 13C NMR (75 MHz, CD3COCD3): δ 144.1, 143.1, 141.2, 129.5, 128.9, 127.4, 119.2, 114.0, 71.6, 71.3, 70.8, 69.9, 60.5, 54.7, 52.7, 52.4, 47.0. HRMS-FAB Calculated for C29H45O4N4 (MH+) 513.3441; Found MH+ 513.3432.

2. 1H / 13C NMR spectra for 4a-f, 5a-b, 6, 7 and 10a-c.