

## Preparation of N-Aryl Azacrown Ether Derivatives Using Arene-Iron Chemistry

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

$[(\eta^5\text{-Cyclopentadienyl})(\eta^6\text{-}(1\text{-}(4\text{-hydroxypiperazino})\text{-}4\text{-}(4,7,10,13\text{-tetraoxa-}1\text{-azacyclopentadecyl))\text{benzene})]\text{iron Hexafluorophosphate (3b)}$  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  $\text{CH}_3\text{CN}$  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  $\times$  2) to remove excess crown ether and 4-hydroxypiperazine, and the crude product was submitted to demetallation.  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  5.74 (4H, s), 4.95 (5H, s). HRMS–FAB: Calculated for  $\text{C}_{26}\text{H}_{39}\text{O}_5\text{N}_2\text{Fe}$  515.2208; Found 515.2201.

$1\text{-}(4\text{-Hydroxypiperazino})\text{-}4\text{-}(4,7,10,13\text{-tetraoxa-}1\text{-azacyclopentadecyl))\text{benzene (4b)}$  The crude **3b** was dissolved in 50 mL  $\text{CH}_3\text{CN}$ , 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/ $\text{Et}_3\text{N}$ : 1/2/0.1,  $R_f$  = 0.2), to afford the product as a colorless oil (140 mg, overall yield from **1** is 77%).  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  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  $\text{C}_{21}\text{H}_{34}\text{O}_5\text{N}_2$  394.2468; Found 394.2469.

$[(\eta^5\text{-Cyclopentadienyl})(\eta^6\text{-}(1\text{-chloro-}4\text{-}(4,7,10,13,16\text{-pentaoxa-}1\text{-azacyclopentadecyl))\text{benzene})]\text{iron Hexafluorophosphate (2b)}$  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  $\times$  3) to remove most of the excess crown ether. The crude product was used for preparing complex **3c**.  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  6.39 (2H, s), 6.03 (2H, s), 5.04 (5H, s). HRMS–FAB: Calculated for  $\text{C}_{23}\text{H}_{33}\text{O}_5\text{NClFe}$  494.1397; Found 494.1373.

$[(\eta^5\text{-Cyclopentadienyl})(\eta^6\text{-}(1\text{-}(4\text{-piperazino})\text{-}4\text{-}(4,7,10,13,16\text{-pentaoxa-}1\text{-azacyclopentadecyl))\text{benzene})]\text{iron Hexafluorophosphate (3c)}$  To a solution of complex **2b** (380 mg, 0.5 mmol) in 20 mL  $\text{CH}_3\text{CN}$  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.  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  5.71 (4H, s), 4.95 (5H, s). HRMS–FAB: Calculated for  $\text{C}_{27}\text{H}_{42}\text{O}_5\text{N}_3\text{Fe}$  544.2474; Found 544.2478.

$1\text{-}(4\text{-Piperazino})\text{-}4\text{-}(4,7,10,13,16\text{-pentaoxa-}1\text{-azacyclopentadecyl))\text{benzene (4c)}$  The above crude product **3c** was dissolved in 50 mL  $\text{CH}_3\text{CN}$ , 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,  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{Et}_3\text{N}$ : 100/5/5,  $R_f$  = 0.3), to afford **4c** as a red oil (143 mg, 77% overall yield from **1**).  $^1\text{H}$  NMR (200 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  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).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  144.5, 143.6, 119.3, 114.0, 71.7, 71.6, 71.5,

07.7, 52.7, 52.8, 71.2. HRMS-FAB Calculated for  $C_{22}H_{30}O_3N_3Fe$  (MH<sup>+</sup>) 424.2793; Found 424.2793.

[( $\eta^5$ -Cyclopentadienyl)( $\eta^6$ -(1-chloro-4-(4,10,13-trioxa-1,7-diazacyclopentadecyl))benzene)]iron Hexafluorophosphate (**2c**) To a round-bottom flask was added **1** (357 mg, 0.86 mmol), and 1,7-diaza-15-crown-5 (565 mg, 2.6 mmol). The flask was flushed with argon, and pyridine (0.5 mL, 6 mmol) 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  $\times$  3). The crude product was divided into two portions and was used immediately for preparing compound **5a** and complex **3d**. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  6.52 (2H, d, J = 7.2), 6.14 (2H, d, J = 7.2), 5.12 (5H, s). HRMS-FAB Calculated for C<sub>21</sub>H<sub>30</sub>O<sub>3</sub>ClFe 449.1295; Found 449.1290.

[( $\eta^5$ -Cyclopentadienyl)( $\eta^6$ -(1-piperidino-4-(4,10,13-trioxa-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. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  5.76 (4H, s), 4.95 (5H, s). HRMS-FAB Calculated for C<sub>26</sub>H<sub>40</sub>O<sub>3</sub>N<sub>3</sub>Fe 498.2419; Found 498.2392.

1-Piperidino-4-(4,10,13-trioxa-1,7-diazacyclopentadecyl)benzene (**4d**) The above complex **3d** (0.62 mmol) was dissolved in 50 mL CH<sub>3</sub>CN, 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, CHCl<sub>3</sub>/CH<sub>3</sub>OH/Et<sub>3</sub>N: 180/1/20, R<sub>f</sub> = 0.3), to afford **4d** as a pale yellow oil (143mg, 60% overall yield from **1**). <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  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). <sup>13</sup>C NMR (50 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  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 C<sub>21</sub>H<sub>36</sub>O<sub>3</sub>N<sub>3</sub> (MH<sup>+</sup>) 378.2756; Found MH<sup>+</sup> 378.2756.

Cyclopentadienyl)( $\eta^6$ -(1-chloro-4-(4,7,13,16-tetraoxa-1,10-diazacyclooctadecyl))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. <sup>1</sup>H NMR showed no SM, the reaction was carried on for preparing **5b** directly. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>):  $\delta$  6.53 (2H, d, J = 7.2), 6.07 (2H, d, J = 7.2), 5.1 (5H, s). HRMS-FAB Calculated for C<sub>23</sub>H<sub>34</sub>O<sub>4</sub>N<sub>2</sub>ClFe 493.1556; Found 493.1575.

1-Chloro-4-(4,7,13,16-tetraoxa-1,10-diazacyclooctadecyl)benzene (**5b**) Complex **2d** (beginning with 0.13 mmol **1**) was dissolved in 40 mL CH<sub>3</sub>CN, 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, CH<sub>3</sub>Cl/Et<sub>3</sub>N: 10/1, R<sub>f</sub> = 0.3), to afford **5b** as pale yellow oil (20 mg, 77% overall yield from **1**). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  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). <sup>13</sup>C NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  146.6, 129.0, 120.6, 112.8, 70.6, 70.5, 70.5, 68.6, 50.8, 49.4. HRMS-FAB Calculated for C<sub>18</sub>H<sub>30</sub>O<sub>4</sub>N<sub>2</sub>Cl (MH<sup>+</sup>) 373.1894; Found MH<sup>+</sup> 373.1891.

[( $\eta^5$ -Cyclopentadienyl)( $\eta^6$ -(1-piperidino-4-(4,7,13,16-tetraoxa-1,10-diazacyclooctadecyl))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 CH<sub>3</sub>CN were removed by rotary evaporation. Without further purification, the crude product was submitted directly to demetallation. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>)  $\delta$  5.8 (4H, q, J = 7.6), 5.0 (5H, s). HRMS-FAB Calculated for C<sub>28</sub>H<sub>44</sub>O<sub>4</sub>N<sub>3</sub>Fe 542.2681; Found 542.2676.

complex **3e** was dissolved in 45 mL CH<sub>3</sub>CN, 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, CH<sub>3</sub>OH(NH<sub>3</sub>)/Et<sub>2</sub>O:1/4, R<sub>f</sub> = 0.2), to afford **4e** as pale yellow oil (114 mg, 65% overall yield from **1**). <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 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). <sup>13</sup>C NMR (50 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 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 C<sub>23</sub>H<sub>40</sub>O<sub>4</sub>N<sub>3</sub> (MH<sup>+</sup>) 422.3019; Found MH<sup>+</sup> 422.3010.

[(η<sup>5</sup>-Cyclopentadienyl)(η<sup>6</sup>-(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 CH<sub>3</sub>CN 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. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 5.50 (4H, q), 4.75 (5H, s). HRMS – FAB: Calculated for C<sub>28</sub>H<sub>46</sub>O<sub>5</sub>N<sub>3</sub>Fe 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 CH<sub>3</sub>CN, 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/CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH/Et<sub>3</sub>N: 60/120/10/10, R<sub>f</sub> = 0.3), to afford **4f** as a pale red oil (33 mg, 75% overall yield from **1**). <sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>): 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). <sup>13</sup>C NMR (50 MHz, C<sub>6</sub>D<sub>6</sub>): 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 C<sub>23</sub>H<sub>40</sub>O<sub>5</sub>N<sub>2</sub> (MH<sup>+</sup>) 438.2968; Found MH<sup>+</sup> 438.2963.

[(η<sup>5</sup>-Cyclopentadienyl)(η<sup>6</sup>-(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 CH<sub>3</sub>CN, and piperazine (193 mg, 2.3 mmol) was added. The mixture was heated to reflux overnight, then cooled and filtered through Celite. CH<sub>3</sub>CN 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. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 7.41 (s), 5.70 (4H, br s), 4.95 (5H, s). HRMS-FAB Calculated for C<sub>34</sub>H<sub>47</sub>O<sub>5</sub>N<sub>4</sub>Fe 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 CH<sub>3</sub>CN, 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/Et<sub>3</sub>N/CH<sub>3</sub>OH: 10/1/1, R<sub>f</sub> = 0.2), to afford **10b** as red orange oil (66 mg, 56% overall yield from **1**). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 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). <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>COCD<sub>3</sub>): 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 C<sub>29</sub>H<sub>43</sub>O<sub>5</sub>N<sub>4</sub> (MH<sup>+</sup>) 527.3233; Found MH<sup>+</sup> 527.3233.

[(η<sup>5</sup>-Cyclopentadienyl)(η<sup>6</sup>-(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 CH<sub>3</sub>CN, piperazine (6 equiv) was added, the mixture was heated to reflux overnight, then filtered through Celite. CH<sub>3</sub>CN was removed by rotary evaporation, and the residue was washed with ether. Without further purification, the dark-red residue was submitted directly to demetallation. <sup>1</sup>H NMR (200 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 5.73 (4H, br s), 4.97 (5H, s). HRMS-FAB Calculated for C<sub>34</sub>H<sub>49</sub>O<sub>4</sub>N<sub>4</sub>Fe 633.3103; 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 CH<sub>3</sub>CN, and irradiated with 100 W Q-beam halogen lamp for 30 min. The solvent was removed by rotary evaporation, and the residue was purified

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





















