Supporting Information

Cobalt (III) Complexes as Novel Matrix Metalloproteinase-9 Inhibitors

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Synthesis and Characterization

(*S*)-Methyl 2-(benzyloxycarbonylamino)-6-(*tert*-butoxycarbonylamino)hexanoate (4). A mixture of Cbz-Lys(Boc)-OH (721 mg, 1.9 mmol), methanol (74 mg, 2.3 mmol), and DMAP (28 mg, 0.23 mmol) in dichloromethane (10 mL) was treated with DCC (1 M in dichloromethane, 2.3 mL). The mixture was stirred at room temperature for 2 h then concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with hexane:ethylacetate (3:2) as an eluent to obtain **4** as a colorless oil (707 mg, 94%).

^{1}H NMR (500 MHz, chloroform-*d*) δ7.38 (5H, s, aryl), 5.47 (1H, s, NH), 5.12 (2H, s, CH_2Ph), 4.63 (1H, s, NH), 3.75 (3H, s, OCH_3), 3.72 (1H, m, CH), 3.11 (2H, bs, CH_2NH), 1.85 (2H, bs, C$\underline{H}_2$CH), 1.3-1.4 (13H, m, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$, *t*-butyl); ^{13}C NMR (126 MHz, chloroform-*d*) δ 173.20, 156.35, 136.49, 128.76, 128.40, 79.37, 67.23, 53.95, 52.63, 40.22, 32.33, 29.80, 28.65, 22.58.

(*S*)-Benzyl 1-hydroxyhexan-6-(*tert*-butoxycarbonylamino)-2-ylcarbamate (5). A solution of **4** (707 mg, 1.8 mmol) in THF (10 mL) was treated with lithium borohydride (2 M in THF) at 0 °C. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was diluted with ethyl acetate, and quenched with water. The organic layer was separated and 10% phosphoric acid was added slowly. The organic layer was then separated again and washed with a saturated solution of sodium bicarbonate and brine successively. The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography with hexane:ethylacetate (2:3) as an eluent to afford **5** as a yellow oil (568 mg, 86%).

^{1}H NMR (500 MHz, chloroform-*d*) δ 7.34 (5H, s, aryl), 5.1 (3H, m, NH and CH_2Ph), 4.62 (1H, s, NH), 3.63 (3H, m, C$\underline{H}$C$\underline{H}_2$OH), 3.07 (2H, bs, CH_2NH), 1.57 (2H, bs, C$\underline{H}_2$CH), 1.2-1.4 (13H, m, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$, *t*-butyl); ^{13}C NMR (126 MHz, chloroform-*d*) δ 157.02, 136.69, 128.77, 128.38, 79.56, 67.04, 65.12, 53.22, 39.87, 30.72, 30.19, 28.66, 22.84.

(*S*)-Benzyl 1-azidohexan-6-(*tert*-butoxycarbonylamino)-2-ylcarbamate (6). A solution of **5** (568 mg, 1.55 mmol), triethylamine (0.25 mL, 2.01 mmol) in toluene (5 mL) was treated with methanesulfonyl chloride (0.14 mL, 2.01 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. After the disappearance of starting material based on TLC, a mixture of sodium azide (445 mg, 6.85 mmol) and tetrabutyl ammonium bromide (59 mg, 0.18 mmol) in water (0.5 mL) was added to the reaction mixture. The reaction mixture was heated at 70 °C overnight. After cooling down to room temperature, the mixture was diluted with water and extracted with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel with hexane: ethylacetate (3:2) as an eluent to afford **6** as a yellow oil (558 mg, 92%).

^{1}H NMR (500 MHz, chloroform-*d*) δ 7.34 (5H, s, aryl), 5.09 (2H, s, CH_2Ph), 5.01 (1H, m, NH), 4.60 (1H, s, NH), 3.75 (1H, bs, CH), 3.4 (2H, m, CH_2N_3), 3.08 (2H, bs, CH_2NH), 1.3-1.6 (15H, m, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH, *t*-butyl); ^{13}C NMR (126 MHz, chloroform-*d*) δ 156.38, 136.56, 128.81, 128.40, 79.44, 67.15, 55.01, 50.98, 40.22, 31.92, 30.04, 28.67, 23.12; ESI-MS *m/z* $[M+Na]^+$: 414.1.

(*S*)-Benzyl 2-azido-6-(biphenyl-4-ylsulfonamido)hexylcarbamate (7). A solution of **6** (279 mg, 0.72 mmol) in trifluoroacetic acid (5 mL) was stirred at room temperature for 1 h. The reaction was monitored by TLC and the solution was concentrated under reduced pressure to afford deprotected amine as a brown solid. The crude solid was dissolved in a saturated solution of sodium bicarbonate (5 mL) and extracted with dichloromethane to obtain the free amine. The combined organic layer was concentrated under reduced pressure. The free amine was dissolved in dichloromethane (5 mL) and treated with triethylamine (0.12 mL, 0.86 mmol) and 4-biphenylsulfonyl chloride (218 mg, 0.86 mmol). The mixture was stirred at room temperature overnight and concentrated. The crude residue was purified by flash column chromatography with hexane:ethylacetate (1:1) as an eluent to afford **7** as a white foam (345 mg, 95%).

^{1}H NMR (500 MHz, chloroform-*d*) δ 7.2-7.9 (13H, m, aryl and biphenyl), 5.10 (2H, s, CH_2Ph), 4.97 (1H, m, NH), 4.10 (1H, s, NH), 3.70 (1H, bs, CH), 3.35 (2H, m, CH_2N_3), 2.93 (2H, bs, CH_2NH), 1.3-1.4 (6H, m, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CH); ^{13}C NMR (126 MHz, chloroform-*d*) δ 156.28, 145.69, 139.45, 138.67, 129.28, 128.77, 128.71, 128.41, 128.29, 127.92, 127.78, 127.51, 67.13, 54.94, 50.77, 43.04, 31.85, 29.25, 22.85; ESI-MS *m/z* $[M+Na]^+$: 531.2.

(*S*)-Benzyl 2-azido-6-biphenyl-4-ylcarboxamidohexyl-

carbamate (8). The free amine was generated from **6** (279 mg, 0.72 mmol) by the procedure described above, and dissolved in dichloromethane (5 mL). The solution was treated with 4-biphenylcarboxylic acid (142 mg, 0.72 mmol) and DCC (1M in dichloromethane, 0.75 mL). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The crude residue was purified by flash column chromatography with hexane: ethylacetate (2:3) as an eluent to afford **8** as a white solid (271 mg, 80%).

^{1}H NMR (500 MHz, chloroform-*d*) δ 7.2-7.8 (13H, m, aryl and biphenyl), 6.63 (1H, s, NH), 5.30 (1H, s, NH), 5.0 (2H, s, CH_2Ph), 4.42 (1H, s, NH), 3.75 (1H, bs, CH), 3.37 (2H, m, CH_2N_3), 2.93 (2H, bs, CH_2NH), 1.3-1.4 (6H, m, $NHCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$); ^{13}C NMR (126 MHz, chloroform-*d*) δ 167.86, 156.46, 144.32, 140.16, 136.57, 133.42, 129.12, 128.75, 128.35, 128.21, 127.77, 127.37, 127.32, 67.02, 55.10, 50.92, 39.54, 34.15, 31.72, 29.40, 22.99; ESI-MS *m/z* $[M+Na]^+$: 494.2.

General Procedure for the Synthesis of 9 and 10. A solution of **7** or **8** in methanol was hydrogenated using palladium on carbon (5 wt %) at 45 psi H_2 for 12 h. The mixture was filtered and concentrated under reduced pressure. The crude mixture was dissolved in ethanol (10 mL) and added slowly to a solution of 2,4-pentanedione over 2 h using a dropping funnel. The mixture was stirred overnight, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel with methanol:dichloromethane (1:20) as an eluent to afford each ligand as a white foam.

***N*-((*S*)-5,6-Bis((*E*)-((*Z*)-4-hydroxypent-3-en-2-ylidene)-amino)hexyl)biphenyl-4-sulfonamide (9).** 168 mg, 48% yield. ^{1}H NMR (500 MHz, chloroform-*d*) δ 10.94 (1H, bs, OH), 10.83 (1H, d, OH, *J* = 5 Hz), 7.90 (2H, d, Ar, *J* = 4 Hz), 7.69 (2H, d, Ar, *J* = 4 Hz), 7.59 (2H, d, Ar, *J* = 3.5 Hz), 7.45 (2H, t, Ar, *J* = 4.7 Hz), 5.91 (1H, m, NH), 4.94 (2H, d, 2 × $C\underline{H}$=C(OH)CH_3), 3.53 (1H, m, $NC\underline{H}CH_2$), 3.24 (2H, m, CH_2N), 2.94 (2H, d, CH_2NHSO_2), 1.97 (6H, s, 2 × C(OH)CH_3), 1.84 (3H, s, CHN=CC$\underline{H}_3$), 1.81 (3H, s, CH_2N=CC$\underline{H}_3$), 1.2-1.4 (6H, m, $NHCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$); ^{13}C NMR (126 MHz, chloroform-*d*) δ 195.62, 195.49, 163.52, 163.32, 145.48, 139.55, 139.06, 129.26, 129.11, 128.65, 127.86, 127.78, 127.52, 96.29, 54.52, 48.60, 42.88, 33.01, 29.93, 29.13, 22.92, 19.30, 18.93; ESI-MS *m/z* $[M+H]^+$: 512.2 $[M+Na]^+$: 534.2.

***N*-((*S*)-5,6-Bis((*E*)-((*Z*)-4-hydroxypent-3-en-2-ylidene)-amino)hexyl)biphenyl-4-carboxamide (10).** 247 mg, 90% yield. ^{1}H NMR (500 MHz, chloroform-*d*) δ 11.02 (1H, bs, OH), 10.96 (1H, d, OH, *J* = 4.5 Hz), 7.90 (2H, d, Ar, *J* = 4 Hz), 7.65 (2H, d, Ar, *J* = 4 Hz), 7.61 (2H, d, Ar, J = 3.75 Hz), 7.46 (2H, t, Ar, *J* = 5.2 Hz), 6.86 (1H, m, NH), 4.97 (2H, d, 2 × $C\underline{H}$=C(OH)CH_3), 3.58 (1H, m, $NC\underline{H}CH_2$), 3.47 (2H, q, *J* = 4.75 Hz, CH_2N), 3.30 (2H, d, CH_2NHCO), 1.99 (6H, d, 2 × C(OH)CH_3), 1.89 (3H, s, CHN=CC$\underline{H}_3$), 1.86 (3H, s, CH_2N=CC$\underline{H}_3$), 1.2-1.4 (6H, m, $NHCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$); ^{13}C NMR (126 MHz, chloroform-*d*) δ 195.71, 167.60, 163.42, 163.19, 144.28, 140.33, 133.59, 129.14, 128.17, 127.83, 127.41, 127.33, 96.39, 54.39, 48.47, 39.56, 32.98, 29.95, 29.14, 22.94, 19.28, 18.92; ESI-MS *m/z* $[M+H]^+$: 476.2 $[M+Na]^+$: 498.2.

General Procedure for the Synthesis of 1-2. To a solution of **9** or **10** in degassed methanol (5 mL) was added cobalt(II) chloride under nitrogen atmosphere. The reaction mixture was heated at 50 °C and stirred for 5 h. A saturated ammonia solution was prepared by bubbling ammonia gas through methanol, and then this saturated solution (5 mL) was added to the reaction mixture. After stirring for 2 h, the reaction mixture was open to air, and approximately 100 mg of charcoal was added to the mixture. Oxygen was bubbled through the reaction mixture overnight. The mixture was filtered to remove the charcoal, and concentrated under reduced pressure. The crude residue was purified by column chromatography over activated neutral alumina with methanol:dichloromethane (1:15) to obtain **1** and **2**.

[Co(III)(4-biphenylhexylsulfonylamido)acacen(NH_3)$_2$]Cl (1): Brown solid, 33% yield, ^{1}H NMR (methanol-d_4) δ 7.93 (2H, d, *J* = 4.25 Hz, Ar), 7.83 (2H, d, *J* = 4.25 Hz, Ar), 7.70 (2H, d, *J* = 4.25 Hz, Ar), 7.4-7.5 (3H, m, Ar), 5.10 (1H, s, $C\underline{H}$=C(OH)CH_3), 5.04 (1H, s, $C\underline{H}$=C(OH)CH_3), 3.75 (1H, m, $NC\underline{H}CH_2$), 3.67 (2H, d, *J* = 7 Hz, CH_2N=C), 2.93 (2H, m, $C\underline{H}_2NHSO_2$), 2.29 (3H, s, C(OH)CH_3), 2.27 (3H, s, C(OH)CH_3), 2.12 (3H, s, CHN=CC$\underline{H}_3$), 2.11 (3H, s, CH_2N=CC$\underline{H}_3$), 1.3-1.6 (6H, m, $NHCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$); ^{13}C NMR (126 MHz, methanol-d_4) δ 178.06, 177.43, 177.08, 169.73, 169.34, 145.35, 139.40, 129.03, 128.41, 127.49, 127.12, 98.17, 63.95, 57.16, 44.10, 33.46, 26.11, 24.42, 21.52, 21.39; ESI-MS *m/z* $[M-2NH_3]^+$: 568.1.

[Co(III)(4-biphenylhexylamido)acacen(NH_3)$_2$]Cl (2): Brown solid, 75% yield, ^{1}H NMR (methanol-d_4) δ 7.97 (2H, d, *J* = 4.25 Hz, Ar), 7.74 (2H, d, *J* = 4.25 Hz, Ar), 7.67 (2H, d, *J* = 3.75 Hz, Ar), 7.4-7.5 (3H, m, Ar), 5.08 (1H, s, $C\underline{H}$=C(OH)CH_3), 5.05 (1H, s, $C\underline{H}$=C(OH)CH_3), 3.79 (1H, m, $NC\underline{H}CH_2$), 3.65 (2H, d, *J* = 7 Hz, CH_2N=C), 3.45 (2H, m, $C\underline{H}_2NHCO$), 2.29 (3H, s, C(OH)CH_3), 2.21 (3H, s, C(OH)CH_3), 2.13 (3H, s, CHN=CC$\underline{H}_3$), 2.11 (3H, s, CH_2N=CC$\underline{H}_3$), 1.4-1.7 (6H, m, $NHCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH$); ^{13}C NMR (126 MHz, methanol-d_4) δ 178.10, 177.42, 170.42, 169.41, 168.47, 144.41, 140.01, 133.10, 128.94, 128.00, 127.91, 126.98, 126.88, 96.96, 63.58, 56.06, 42.66, 39.16, 29.13, 24.48, 24.43, 21.62, 21.46; ESI-MS *m/z* $[M-2NH_3]^+$: 532.2.

6,7-Diazido-heptanoic acid (11). To a mixture of sodium azide (2.23 g, 34.4 mmol) in acetonitrile (40 mL) was added iodine monochloride (2.79 g, 17.2 mmol) at 0 °C. The mixture was stirred for 5 min, and 6-heptenoic acid (2.0 g, 15.6 mmol) was added slowly. The mixture was stirred at room temperature for 20 h. The reaction mixture was poured into water and extracted with diethyl ether. The organic layer was washed with 5% sodium thiosulfate and water, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the crude residue in DMF (20 mL) was added sodium azide (2.3 g, 40.4 mmol). The mixture was heated at 80 °C for 20 h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic layer was washed with water, dried over dried over $MgSO_4$, and

concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel with ethylacetate:hexane (3:2) as an eluent to give **11** as a yellow oil (2.49 g, 87%).

^{1}H NMR (500 MHz, chloroform-*d*) δ 11.2 (1H, bs, COOH), 3.2–3.5 (3H, m, C<u>H</u>C<u>H</u>$_2$N$_3$), 2.38 (2H, t, *J* = 4.8 Hz, C<u>H</u>$_2$CO), 1.4-1.6 (6H, m, NHCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH).

6,7-Diazido-*N*-(biphenyl-4-ylmethyl)heptanamide (12). A solution of **11** (2.49 g, 29.9 mmol), biphenyl methylamine **16** (3.22 g, 44.9 mmol) and DMAP (366 mg, 3 mmol) in dichloromethane (50 mL) was treated with DCC (1 M solution in dichloromethane, 36 mL). After stirring at room temperature for 3 h, the mixture was concentrated under reduced pressure and purified by flash column chromatography using hexane:ethylacetate (2:3) as an eluent to afford **12** as a yellow oil (4.28 g, 96%).

^{1}H NMR (chloroform-*d*) δ 7.59-7.36 (9H, m, biphenyl), 5.76 (1H, bs, NH), 4.50 (2H, d, CH$_2$Ar, *J* = 5.5 Hz), 3.48 (1H, m, CHN$_3$), 3.3-3.4 (m, 2H, CH$_2$N$_3$), 2.27 (2H, t, *J* = 7.5 Hz, CH$_2$CO), 1.4-1.6 (6H, m, NHCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH); ESI-MS *m/z* [M+Na]$^+$: 400.2.

***N*-(Biphenyl-4-ylmethyl)-6,7-bis((*E*)-((*Z*)-4-hydroxypent-3-en-2-ylidene)amino) heptanamide (13).** A mixture of **12** (4.28 g, 28.7 mmol) in methanol (150 mL) was hydrogenated using palladium on carbon (5 wt %) at 45 psi H_2 for 12 h. The mixture was filtered and concentrated under reduced pressure. The crude mixture was dissolved in ethanol (50 mL) and added slowly to a solution of 2,4-pentanedione over 2 h using a dropping funnel. The mixture was stirred overnight and concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel with methanol:dichloromethane (1:20) as an eluent to afford **13** as a white solid (3.85 g, 69%).

^{1}H NMR (chloroform-*d*) δ 10.97 (1H, s, OH), 10.86 (1H, d, *J* = 5 Hz, OH), 7.55 (5H, m, Ar), 7.43 (2H, t, *J* = 5.2 Hz, Ar), 7.33 (2H, d, *J* = 1.75 Hz), 6.57 (1H, s, NH), 4.95 (2H, d, 2 × C<u>H</u>=C(OH)CH$_3$), 4.45 (2H, d, *J* = 5.5 Hz, CH$_2$Ar), 3.51 (1H, m, NC<u>H</u>CH$_2$), 3.25 (2H, m, CH$_2$N=C), 2.24 (2H, m, CH$_2$NHCO), 1.98 (6H, s, 2 × C(OH)CH$_3$), 1.87 (3H, s, CHN=CC<u>H</u>$_3$), 1.83 (3H, s, CH$_2$N=CC<u>H</u>$_3$), 1.2-1.6 (6H, m, NHCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH); ^{13}C NMR (126 MHz, chloroform-*d*) δ 195.62, 172.86, 163.31, 163.00, 140.83, 140.40, 137.78, 128.94, 128.42, 127.45, 127.15, 96.25, 54.13, 48.43, 43.33, 36.07, 34.10, 32.80, 29.05, 25.25, 19.20, 18.84; ESI-MS *m/z* [M+H]$^+$: 490.3 [M+Na]$^+$: 512.3.

[Co(III)(4-biphenylmethyl-heptylamido)acacen(NH$_3$)$_2$]Cl (3). Compound **3** was synthesized by following the same procedure described for the synthesis of **1** and **2**.

Brown solid, 76% yield, ^{1}H NMR (methanol-d_4) δ 7.6 (4H, t, *J* = 4.5 Hz, Ar), 7.3-7.4 (5H, m, Ar), 5.09 (1H, s, C<u>H</u>=C(OH)CH$_3$), 5.04 (1H, s, C<u>H</u>=C(OH)CH$_3$), 4.42 (2H, s, CH$_2$Ar), 3.74 (1H, m, NC<u>H</u>CH$_2$), 3.64 (2H, d, *J* = 6.75 Hz, CH$_2$N=C), 2.33 (2H, m, C<u>H</u>$_2$NHCO), 2.26 (3H, s, C(OH)CH$_3$), 2.23 (3H, s, C(OH)CH$_3$), 2.12 (3H, s, CHN=CC<u>H</u>$_3$), 2.11 (3H, s, CH$_2$N=CC<u>H</u>$_3$), 1.3-1.7 (6H, m, NHCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$CH); ^{13}C NMR (126 MHz, methanol-d_4) δ 178.37, 177.69, 174.68, 170.27, 169.23, 140.79, 140.11, 138.25, 128.78, 128.03, 127.25, 126.91, 126.72, 96.86, 95.94, 63.46, 56.06, 42.58, 35.54, 26.75, 25.64, 24.46, 21.55, 21.38; ESI-MS *m/z* [M-2NH$_3$]$^+$: 546.2.

Biphenyl-4-carboxylic acid (14). To a cooled solution of Jones reagent (1.33 M, 10.83 mL) in acetone (10 mL) was added a solution of 4-biphenyl methanol (1.0 g, 5.43 mmol) in acetone (1 mL). The mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC, and the mixture was decanted into diethyl ether and saturated sodium bisulfite solution. The ether layer was separated and concentrated under reduced pressure to obtain **14** as a white solid (995 mg, 97%).

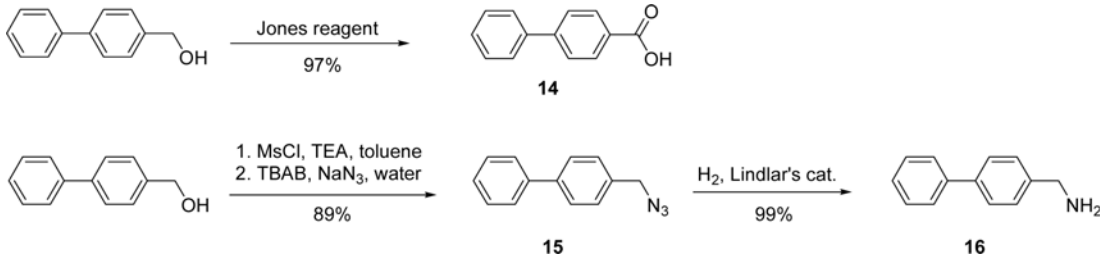
^{1}H NMR (chloroform-*d*) δ 8.21 (2H, d, *J* = 4 Hz, Ar), 7.72 (2H, d, *J* = 4 Hz, Ar), 7.66 (2H, d, *J* = 3.75 Hz), 7.46 (3H, m, Ar); ^{13}C NMR (126 MHz, chloroform-*d*) δ 171.44, 146.77, 140.13, 131.02, 129.23, 128.56, 128.14, 127.59, 127.44.

4-(Azidomethyl)biphenyl (15). Compound **15** was synthesized from 4-biphenyl methanol (506 mg, 2.71 mmol) by following the same procedure described for the synthesis of **6** (505 mg, 89%).

^{1}H NMR (chloroform-*d*) δ 7.3-7.6 (9H, m, Ar), 4.45 (2H, s, CH$_2$N$_3$); ^{13}C NMR (126 MHz, chloroform-*d*) δ 141.18, 140.48, 132.42, 128.91, 128.72, 127.58, 127.55, 127.13, 54.47.

Biphenyl-4-ylmethanamine (16). A solution of **15** (505 mg, 2.42 mmol) in ethanol (100 mL) was hydrogenated using Lindlar's catalyst and a hydrogenator (40 psi H_2). After stirring for 2 h, the mixture was filtered to remove the catalyst, and concentrated under reduced pressure to obtain **16** as a white solid. (446 mg, 99%).

^{1}H NMR (chloroform-*d*) δ 7.3-7.6 (9H, m, Ar), 3.93 (2H, s, CH$_2$NH$_2$); ^{13}C NMR (126 MHz, chloroform-*d*) δ 128.97, 127.75, 127.53, 127.40, 127.72, 46.42.



Scheme S1. Synthesis of biphenyl fragments.