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TETRAHEDRON: *ASYMMETRY*

Synthesis of homochiral pentadentate sulfonamide-based ligands

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Abstract—A two-step synthesis of pentadentate, tetraionic ligands based on sulfonamide, amide, and pyridyl groups is reported. These ligands are easily accessible in good to excellent yield from commercially available materials.

1. Introduction

The development of novel chiral ligands is crucial to the advancement of asymmetric catalysis. Classification of ligands that have been successfully used in enantioselective catalysis by denticity, that is the number of points of attachment of the ligand to the metal and by the formal charge of the closed shell form of the ligand, can be informative. Many of the most common ligands are bidentate and neutral, including chelating phosphines such as DIOP and BINAP.[1] Others like TADDOL[2–5] and BINOL[6,7] are bidentate and dianionic. Ligands of higher denticity have been less well developed. One of the most useful classes of ligands is the tetradentate salen ligands, which have been successfully employed in asymmetric epoxidation[8–10] and asymmetric epoxide ring opening reactions,[11–13] for example. Chiral tetradentate, dianionic porphyrin ligands have also been used with great success in asymmetric oxidation reactions.[14–22] Other tetradentate dianionic[23–29] and trianionic ligands also are promising.[30,31] Chiral tetradentate[32–34] and pentadentate tetraanionic ligands are an under represented class of ligands in asymmetric catalysis despite the use of achiral analogs in stabilizing reactive metal centers.[35–39]

The goal of the work reported herein is to design pentadentate tetraionic ligands for use in asymmetric catalysis. It was envisaged that a pentadentate ligand could coordinate to metals and leave an open coordination site that could bind and activate a substrate in a Lewis acid catalyzed reaction. The core of the ligand is based on the pyridine bis(amide), which is known to bind well to transition metal complexes, as shown in Fig. 1.[40]

The synthesis of the ligands was realized in two easy steps as outlined in Eqs. (1) and (2). The first step is identical to that used in the synthesis of sulfonamide/Schiff base ligands that have been used in the asymmetric cyclopropanation of allylic alcohols.[41,42] Dissolving the tartrate salt of (*R*,*R*)-*trans*-1,2-diaminocyclohexane in water with two equivalents of NaOH followed by addition of dichloromethane, triethylamine, and a sulfonyl chloride led to the formation of the amino-sulfonamides. The work-up procedure involved acidic extraction followed by raising the pH of the solution to 9. Using this procedure any bis(sulfonamide) complex formed was easily removed.[42]

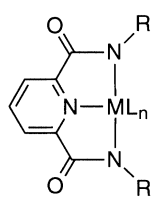

Figure 1.

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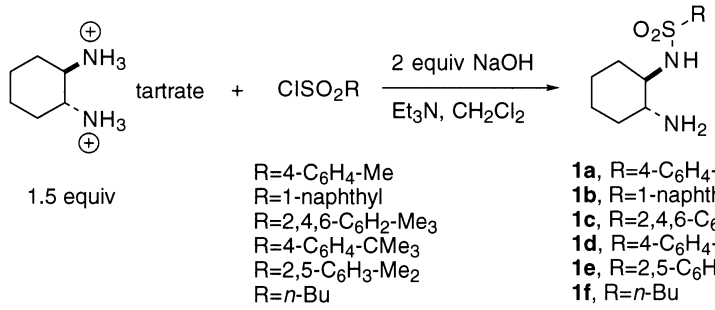
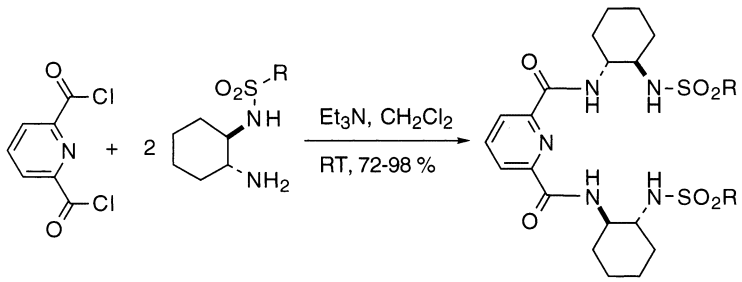


(1)

The amino-sulfonamides were then treated with 0.5 equivalent of 2,6-pyridinedicarbonyl dichloride in dichloromethane in the presence of triethylamine to furnish the pyridyl bis(amide) bis(sulfonamide) ligands, as shown in Eq. (2).



(2)

These ligands are easily synthesized and should readily bind to transition metal complexes to provide chiral Lewis acids for use in asymmetric catalysis. This work is currently being pursued in our laboratories.

2. Experimental

2.1. Synthesis of 1a–1f

The procedures used to synthesize compounds **1a**–**1f** were identical to that described for **1a**. The syntheses of **1a**–**1f** have been improved since our original report.[42]

To a stirred solution of L-tartrate salt of (*R*,*R*)-1,2-diaminocyclohexane (3.00 g, 11.36 mmol) in aqueous NaOH (2N, 15 mL) was added triethylamine (2.1 mL, 15.2 mmol) and dichloromethane (110 mL). The mixture was cooled to 0°C and a solution of *p*-toluene sulfonyl chloride (1.44 g, 7.6 mmol) in dichloromethane (76 mL) was added dropwise over 30 min. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 12 h. The resulting reaction mixture was washed with aqueous HCl (2N, 3×50 mL) and the organic phase was removed. The HCl wash liquor was collected and adjusted to pH 9 by adding NaOH pellets. The basic aqueous solution was then extracted with dichloromethane (3×30 mL). The dichloromethane layers were combined, dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to obtain **1a** as a pale yellow solid (2.01 g, 7.55 mmol, 99%). The characterization of these compounds has been previously reported.[42]

2.2. Synthesis and characterization of 2a–2f

The preparation of **2a** is described below. Compounds **2b**–**2f** were prepared using this procedure.

To a stirred solution of **1a** (1.00 g, 3.73 mmol) in dichloromethane (30 mL) was added 2,6-pyridinedicarbonyl dichloride (0.38 g, 1.87 mmol) in dichloromethane (25 mL) and triethylamine (0.52 mL, 3.74 mmol). The mixture was stirred at room temperature for 12 h. The resulting solution was washed with water (3×50 mL). The organic layer was collected and anhydrous $MgSO_4$ was added. The solution was filtered and the solvent was removed under reduced pressure.

Data for 2a: The yield was 72% (0.95 g, 1.35 mmol). The white solid obtained from the filtrate was purified by column chromatography using silica. Compound **2a** was eluted using chloroform/ethyl acetate (1:1, v/v). Mp 262–263°C; $[\alpha]_D = -171.6$ ($c = 1.2$ g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.1 (m, 2H), 1.22 (m, 2H), 1.28 (m, 2H), 1.35 (m, 2H), 1.63 (d, $J = 10.4$ Hz, 4H), 1.82 (d, $J = 8.3$ Hz, 2H), 2.24 (m, 8H), 3.25 (m, 2H), 3.78 (m, 2H), 5.20 (d, $J = 6.3$ Hz, 2H), 7.07 (d, $J = 8.3$ Hz, 4H), 7.65 (d, $J = 8.3$ Hz, 4H), 7.96 (t, $J = 6.3$ Hz, 1H), 8.2 (d, $J = 6.3$ Hz, 2H), 8.5 (d, $J = 6.3$ Hz, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 50 MHz) δ 21.4, 24.3, 25.0, 32.0, 34.2, 53.7, 57.4, 124.5, 126.6, 129.5, 138.4, 138.6, 143, 148.5, 164.3 ppm. IR (KBr) 3340, 3279, 3133, 2933, 2856, 2350, 1671, 1544, 1452, 1329, 1160,

1083, 886, 800, 729, 700, 676, 557 cm^{-1}; high resolution mass spectrum m/z 690.2386 [M+Na^+; calcd for $C_{33}H_{41}N_5O_6S_2Na$: 690.2395].

Data for 2b: The yield was 80% (1.00 g, 1.37 mmol). The pale yellow solid obtained from the filtrate was purified by column chromatography using silica. Compound **2b** was eluted using methanol/hexane/dichloromethane (1:1:1 v/v). Mp 187–188°C; $[\alpha]_D = 31.9$ ($c = 0.0475$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.0 (tq, $J_1 = 2.2$ Hz, $J_2 = 10.5$ Hz, 2H), 1.22 (tq, $J_1 = 2.2$ Hz, $J_2 = 11.9$ Hz, 2H), 1.28 (dq, $J_1 = 2.2$ Hz, $J_2 = 11.9$ Hz, 2H), 1.43 (dq, $J_1 = 2.2$ Hz, $J_2 = 11.9$ Hz, 2H), 1.54 (d, $J = 10.5$ Hz, 2H), 1.6 (d, $J = 10.5$ Hz, 2H), 1.68 (d, $J = 10.5$ Hz, 2H), 2.24 (d, $J = 10.5$ Hz, 2H), 3.22 (m, 2H), 3.78 (m, 2H), 5.5 (d, $J = 5.1$ Hz, 2H), 7.36 (t, $J = 6.3$ Hz, 2H), 7.48 (t, $J = 6.3$ Hz, 2H), 7.56 (t, $J = 6.3$ Hz, 2H), 7.70 (*d*, $J = 7.0$ Hz, 2H), 7.86 (t, $J = 6.3$ Hz, 1H), 7.96 (d, $J = 7.0$ Hz, 2H), 8.60 (d, $J = 7.0$ Hz, 2H), 8.22 (d, $J = 7.0$ Hz, 2H), 8.34 (dd, $J_1 = 1.3$ Hz, $J_2 = 6.3$ Hz, 2H), 8.51 (d, $J = 7.0$ Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 24.4, 25.1, 32.0, 34.1, 53.6, 57.6, 123.8, 124.3, 124.5, 126.8, 127.9, 128.3, 128.7, 129.0, 134.1, 134.2, 135.5, 138.0, 148.2, 164.1 ppm; IR (KBr) 3361, 3340, 2940, 2849, 2372, 1670, 1537, 1460, 1319, 1165, 1123, 1096, 800, 757, 650, 600 cm^{-1}.

Data for 2c: The yield was 81% (0.94 g, 1.22 mmol). The white solid obtained from the filtrate was purified by column chromatography using silica. Compound **2c** was eluted using chloroform/ethyl acetate (1:1, v/v). Mp 167°C; $[\alpha]_D = +37.0$ ($c = 0.072$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (m, 4H), 1.28 (dq, $J_1 = 2.2$ Hz, $J_2 = 11.9$ Hz, 2H), 1.38 (dq, $J_1 = 2.2$ Hz, $J_2 = 11.9$ Hz, 2H), 1.55 (t, $J = 3.1$ Hz, 4H), 1.7 (d, $J = 2.2$ Hz, 2H), 2.0 (s, 6H), 2.15 (d, $J = 2.2$ Hz, 2H), 2.5 (s, 12H), 3.2 (m, 2H), 3.75 (m, 2H), 5.60 (d, $J = 5.0$ Hz, 2H), 6.60 (s, 4H), 7.80 (t, $J = 6.2$ Hz, 1H), 8.15 (d, $J = 7.7$ Hz, 2H), 8.30 (d, $J = 7.7$ Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 20.8, 23.1, 24.5, 25.2, 32.1, 34.0, 53.5, 57.1, 124.6, 131.7, 135.7, 138.0, 138.1, 141.4, 148.2, 164.0 ppm; IR (KBr) 3368, 3237, 2941, 2855, 1683, 1545, 1460, 1328, 1157, 1091, 943, 900, 850, 750, 650, 590, 529 cm^{-1}.

Data for 2d: The yield was 98% (1.78 g, 2.26 mmol). The white solid obtained from the filtrate was purified by column chromatography using silica. Compound **2d** was obtained using chloroform/ethyl acetate (1:1 v/v). Mp 193°C; $[\alpha]_D = +8.3$ ($c = 0.14$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (m, 2H), 1.20 (s, 18H), 1.22 (m, 2H), 1.37 (m, 4H), 1.60 (d, $J = 9.47$ Hz, 4H), 1.75 (d, $J = 9.5$ Hz, 2H), 2.15 (d, $J = 9.5$ Hz, 2H), 3.40 (m, 2H), 3.75 (m, 2H), 5.55 (d, $J = 5.1$ Hz, 2H), 7.25 (d, $J = 7.9$ Hz, 4H), 7.75 (d, $J = 7.9$ Hz, 4H), 7.88 (t, $J = 6.3$ Hz, 1H), 8.15 (d, $J = 7.9$ Hz, 2H), 8.75 (d, $J = 7.9$ Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 24.4, 25.1, 31.1, 32.0, 33.9, 35.0, 53.8, 57.0, 124.5, 125.7, 126.4, 138.4, 138.7, 148.6, 156.0, 164.1 ppm. IR (KBr) 3354, 3172, 2840, 2863, 2400, 1677, 1544, 1453, 1319, 1158, 1074, 829, 750, 629, 571 cm^{-1}; high resolution mass spectrum m/e 774.3326 [M+Na^+; calcd for $C_{39}H_{53}N_5O_6S_2Na$: 7743335].

Data for 2e: The yield was 98% (0.89 g, 2.50 mmol). The white solid obtained from the filtrate was purified by column chromatography using silica. Compound **2e** was obtained using chloroform/ethyl acetate (1:1 v/v). Mp 148°C; $[\alpha]_D = -130.8$ ($c = 0.0395$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (m, 2H), 1.20 (m, 2H), 1.35 (m, 4H), 1.54 (d, $J = 10.7$ Hz, 4H), 1.75 (d, $J = 10.7$ Hz, 2H), 2.10 (d, $J = 10.7$ Hz, 2H), 2.16 (s, 6H), 2.45 (s, 6H), 3.30 (m, 2H), 3.80 (m, 2H), 5.8 (d, $J = 5.1$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 7.00 (d, $J = 8.9$ Hz, 2H), 7.70 (s, 2H), 7.85 (t, $J = 5.6$ Hz, 1H), 8.13 (d, $J = 7.1$ Hz, 2H), 8.60 (d, $J = 7.1$ Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 19.8, 20.7, 24.4, 25.1, 32.1, 33.6, 53.6, 56.7, 124.5, 129.2, 132.4, 133.1, 133.8, 135.6, 138.3, 138.8, 148.5, 164.2 ppm; IR (KBr) 3340, 3200, 2933, 2856, 1674, 1551, 1442, 1321, 1160, 1076, 900, 700, 600 cm^{-1}; high resolution mass spectrum m/z 718.2752 [M+Na^+; calcd for $C_{35}H_{45}N_5O_6S_2Na$: 718.2708].

Data for 2f: The yield was 74% (0.85 g, 1.30 mmol). The white solid was obtained from the filtrate was purified by column chromatography using silica. Compound **2f** was obtained using methanol/ethyl acetate/dichloromethane (1:1:1 v/v). Mp 170°C; $[\alpha]_D = -1.1$ ($c = 0.028$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.75 (t, $J = 6.4$ Hz, 6H), 1.24 (m, 4H), 1.36 (m, 6H), 1.50 (m, 2H), 1.69 (m, 4H), 1.76 (d, $J = 7.3$ Hz, 2H), 1.81 (d, $J = 7.3$ Hz, 2H), 2.17 (d, $J = 10.1$ Hz, 2H), 2.23 (d, $J = 10.1$ Hz, 2H), 2.97 (m, 4H), 3.40 (m, 2H), 3.82 (m, 2H), 5.22 (s, 2H), 7.98 (t, $J = 7.0$ Hz, 1H), 8.27 (d, $J = 7.2$ Hz, 2H), 8.69 (d, $J = 7.2$ Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 13.4, 21.4, 24.5, 25.3, 25.6, 32.2, 34.6, 53.8, 56.7, 56.9, 124.8, 138.8, 148.6, 164.1 ppm; IR (KBr) 3348, 2934, 2861, 2368, 1677, 1552, 1460, 1321, 1137, 1104 cm^{-1}.

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