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# Synthesis of chiral heteroaromatic tetradentate sulfonamide based ligands

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***Abstract:*** We report a facile two step synthesis of chiral tetradentate ligands for late metal complexes. The ligands are easily prepared from *trans*-1,2-diaminocyclohexane or chiral 1,2-diphenylethylenediamine and a heteroaromatic sulfonyl chloride in the presence of base ($K_2CO_3$ or $Et_3N$). These compounds represent a new class of chiral tetradentate $N_2S_2$ and $N_4$ based ligands. © 1997 Elsevier Science Ltd

The demand for functionalized materials of high optical purity has led to an intense research effort in asymmetric synthesis. Much of the attention has focused on the application of chiral main group and transition metal complexes to promote enantioselective transformations. The successful development of asymmetric catalysts is an iterative, multi-step process involving ligand design, catalyst synthesis, and substrate screening. In order to facilitate this process, new ligands which are easily prepared and modified must be advanced. In the realm of tetradentate ligands, the classical example is the salen,[1,2] which serves as a workhorse in inorganic chemistry, as it forms complexes with most d-block elements. The successful application of chiral transition metal based salen complexes in asymmetric epoxidation,[3–6] aziridination[7,8] and epoxide opening[9] clearly demonstrates the exceptional ability of these chiral organic ligands to impart asymmetry when bound to the appropriate metal center.

In this communication, we report the facile synthesis of a new class of chiral tetradentate sulfonamide based ligands containing nitrogen and nitrogen/sulfur. These ligands are designed to bind strongly to late transition metals (Scheme 1). The ligands are synthesized in two steps from commercially available materials.

Sulfonamides, $RSO_2NHR'$, are acidic nitrogen compounds, having $pK_a$s similar to phenols.[10] Therefore, unlike traditional amides ($M–NR_2$),[11] the deprotonated sulfonamide, the sulfonamido, is a poor electron donor due to the strongly electron withdrawing nature of the sulfonyl group. Consequently, the resulting sulfonamido complexes exhibit enhanced Lewis acidity. Additionally, the sulfonamide linkers are remarkably stable, being resistant to hydrolyzing, oxidizing and reducing conditions.[12]

The ligands introduced in this communication contain pyridine, imidazole, benzothiazole and thiophene groups (Scheme 1) that bind to metals through the aromatic nitrogens or sulfurs in addition to the nitrogens of the deprotonated sulfonamide groups.

The synthesis of our new tetradentate ligands is illustrated in Scheme 1. In each case, the synthesis has been done on a multigram scale in several hours. The first step involves the oxidation of the mercapto group to the sulfonyl chloride and is accomplished with either bleach or chlorine gas. We have found that, in the case of 2-mercaptopyridine[13] (**5**) and 2-mercapto-1-methylimidazole (**7**), oxidation can be accomplished efficiently and safely, employing 12% bleach/$H_2SO_4$,[14,15] while 2-mercaptobenzothiazole (**9**) requires chlorine gas (Scheme 1).[16–18] The 2-thiophenesulfonyl chloride (**11**) is commercially available.

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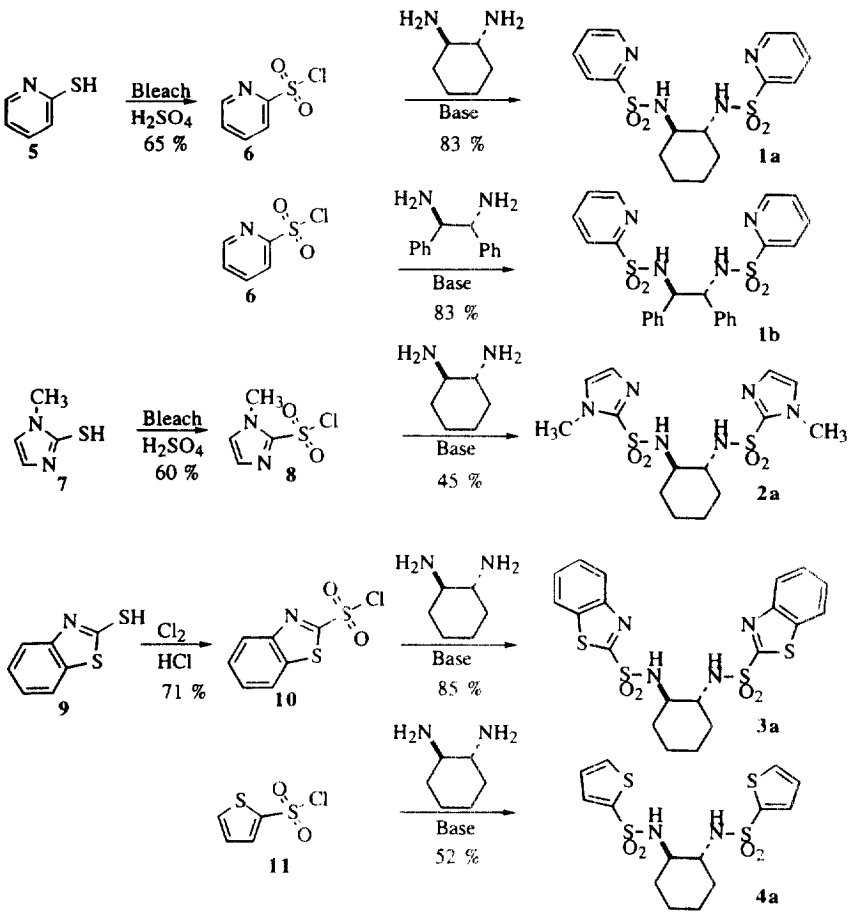


**Scheme 1.**

The final step involves the reaction of the resulting sulfonyl chlorides **6**, **8**, **10** and **11** with the chiral *trans*-1,2-diaminocyclohexane,[19,20] in the presence of base, to provide ligands **1a–4a** in 83, 45, 85, and 52% recrystallized yield. Reaction of the sulfonyl chloride **6** with (S,S)-1,2-diphenylethylenediamine gave **1b** in 83% yield. The ligands are all crystalline solids that are easily recrystallized from methylene chloride by vapor diffusion of diethyl ether. The crystal structure of **2a** is illustrated in Figure 1 and shows the trans disposition of the diamine.[21]

Many chiral diamines are readily prepared or commercially avaliable and presumably could also be employed in the synthesis of derivatives of these ligands.[22–27] This feature increases the potential utility of our heteroaromatic bissulfonamide ligands.

In summary, we have developed an efficient method to synthesize modular tetradentate sulfonamide based ligands. Compounds containing aromatic nitrogen atoms have an extensive and well documented coordination chemistry.[28] We have circumvented a common problem encountered with imine-based salen ligands. The metal, in these systems, serves to activate the imine, rendering it susceptible to attack. The ligands **1a–4a** incorporate aromatic donor groups which should be less reactive and therefore suppress this degradation pathway. Preliminary results indicate that **1a** readily forms complexes with Cu(II). We are currently exploring the structure of complexes derived from these ligands and will evaluate their use in asymmetric catalysis.

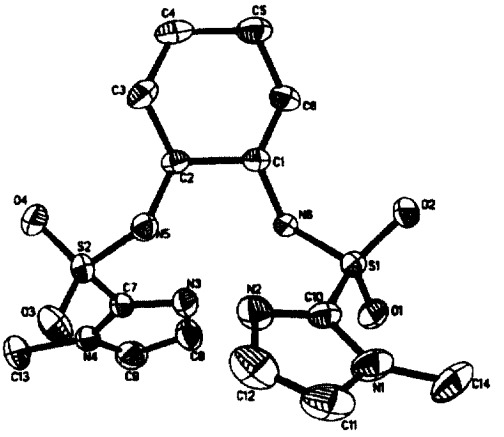


**Figure 1.**


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13. Synthesis of **1a**: the 2-mercaptopyridine **5** (2.00 g, 18.00 mmol) was added to 50 mL of $H_2SO_4$ and cooled to 0°C. Sodium hypochlorite (12%, 112 mL, 180 mmol, 10 eq.) was added dropwise. As the hypochlorite was added, the solution became clear yellow and heat was evolved. The reaction was stirred for 30 min at 0°C. The resulting solution was diluted with water, 30 mL of $CH_2Cl_2$ was added and the layers were separated. The aqueous layer was extracted twice with 20 mL of $CH_2Cl_2$, the organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting sulfonyl chloride, **6**, was dissolved in 30 mL of diethyl ether and cooled to 0°C. $K_2CO_3$ (4 M, 10 mL) was added to the ether solution. *trans*-1,2-Diaminocyclohexane (0.82 g, 7.21 mmol, 0.4 eq) was added slowly. A white precipitate formed almost immediately. The solution was allowed to stir for several hours at 0°C. The crude product was filtered and washed with ether. The product, **1a**, was crystallized from $CH_2Cl_2$ by gas phase diffusion of ether as yellow crystals (1.92 g, 4.86 mmol, 83%). Data for **1a**: mp 155–157°C;

$[\alpha]_D^{25}$=−15.5 (c=1.1, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 200 MHz) δ 8.73 (s (br, NH), 2H), 8.63 (dt, J=4.6 Hz, J=1.5 Hz, 2H), 7.97 (m, 4H), 7.51 (m, 2H), 3.31 (m, 2H), 2.41 (m, 2H), 1.66 (m, 2H), 1.40 (m, 2H), 1.20 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 60 MHz) δ 158.6, 148.3, 139.4, 127.0, 122.6, 57.4, 35.4, 24.1; IR (KBr) 3420, 3056, 2962, 2865, 1488, 1396, 1323, 1274, 1047, 904, 760, 702 $cm^{-1}$; MS (FAB, NBA) 397 ($MH^+$). Data for **1b**: mp 223–225°C; $[\alpha]_D^{25}$=−31.3 (c=1.1, $CH_3OH$); $^1H$ NMR ($CDCl_3$, 200 MHz) δ 7.97 (d, J=3.7 Hz 2H), 7.92 (d, J=4.7 Hz 4H), 7.55 (m, 2H), 7.08 (m, 6H), 6.88 (m, 4H), 5.22 (s (NH, br), 2H) 4.70 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 158.7, 148.7, 139.3, 138.5, 128.1, 127.9, 127.7, 127.0, 122.7, 65.8; IR (KBr) 3429, 3197, 2357, 1648, 1577, 1449, 1322, 1223, 1172, 1068, 952, 698, 597 $cm^{-1}$. Data for **2a**: mp 149–151°C; $[\alpha]_D^{25}$=−24.4 (c=1.2, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 500 MHz) δ 11.36 (s, 2H), 6.99 (d, J=1.1 Hz, 2H), 6.97 (d, J=1.1 Hz, 2H), 3.90 (s, 6H), 3.48 (m, 2H), 2.44 (m, 2H), 1.77 (m, 2H), 1.48 (m, 2H), 1.26 (m, 2H); $^{13}C$ $\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 145.2, 125.2, 123.9, 57.8, 36.2, 34.0, 24.4; IR (KBr) 3049, 2791, 1696, 1484, 1331, 1323, 991, 912, 689 $cm^{-1}$; MS (FAB, NBA) 403 ($MH^+$). Data for **3a**: mp 188–190°C; $[\alpha]_D^{25}$=23.0 (c=1.0, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 200 MHz) δ 8.32 (m, 2H), 7.93 (m, 2H), 7.55 (m, 4H), 4.88 (s, 2H), 3.53 (m, 2H), 2.49 (m, 2H), 1.80 (m, 2H), 1.53 (m, 2H), 1.22 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 60 MHz) δ 168.4, 149.5, 135.9, 128.0, 127.9, 124.9, 122.0, 57.6, 35.7, 24.2; IR (KBr) 3060, 2868, 1472, 1344, 1167, 1092, 761, 617, 569 $cm^{-1}$; MS (FAB, NBA) 509 ($MH^+$). Data for **4a**: mp 167–169°C; $[\alpha]_D^{25}$=−12.8 (c=1.3, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$, 200 MHz) δ 7.75 (dd, J=5.1 Hz, J=1.5 Hz, 2H), 7.61 (dd, J=3.8 Hz, J=1.3 Hz, 2H), 7.15 (dd, J=5.1 Hz, J=3.8 Hz, 2H), 5.74 (s, 2H), 2.88 (m, 2H), 1.77 (m, 2H), 1.55 (m, 2H), 1.15 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 60 MHz) δ 142.8, 134.0, 133.9, 129.3, 58.1, 33.4, 25.1; IR (KBr) 3270, 2929, 2864, 1440, 1407, 1325, 1225, 1150, 1144, 1080, 1011, 893 $cm^{-1}$; MS (FAB, NBA) 407 ($MH^+$)

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