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Synthesis of New Chiral Tetradentate Sulfonamide Based Ligands.

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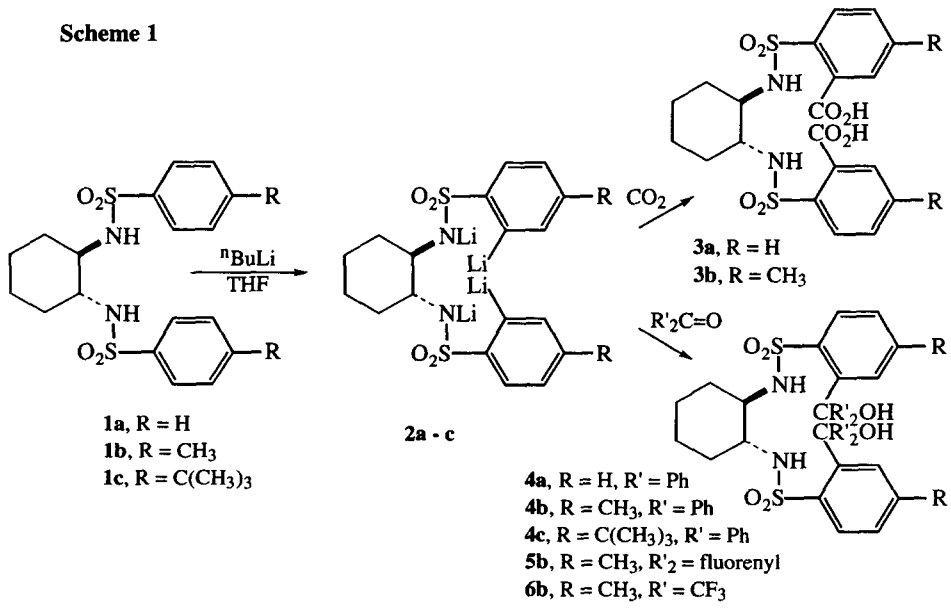
Abstract: *A two step procedure for the synthesis of chiral tetradentate sulfonamide ligands is reported. The ligands are easily prepared from the corresponding bissulfonamide complexes by directed metallation followed by quenching with either ketones or carbon dioxide in 47 to 82 % yield. Preliminary results indicate that these complexes are efficient catalysts in the asymmetric addition of alkyl groups to aldehydes.* © 1997 Elsevier Science Ltd.

The field of catalytic asymmetric synthesis has grown very rapidly in the past fifteen years with new, more powerful methodology being advanced monthly.[1] One of the most important factors in the advancement of catalytic asymmetric processes is the design and development of new chiral ligands. Ideally, the transformations which comprise the ligand synthesis are applicable to a wide variety of substrates in order to synthesize ligands with different steric and electronic properties. Additionally, to be practical, the synthesis must be concise and involve reliable reactions. Working within these constraints, we have prepared a number of elaborate bissulfonamide based tetradentate ligands in *two steps from commercially available materials.*

Scheme 1



1a, R = H
1b, R = CH_3
1c, R = $C(CH_3)_3$

2a - c

3a, R = H
3b, R = CH_3

4a, R = H, R' = Ph
4b, R = CH_3, R' = Ph
4c, R = $C(CH_3)_3$, R' = Ph
5b, R = CH_3, R'$_2$ = fluorenyl
6b, R = CH_3, R' = CF_3

Our starting materials are the bissulfonamides **1a - c** (Scheme 1) which are derived from the readily available *trans*-1,2-diaminocyclohexane. The bissulfonamide complexes can be prepared on multigram scales in several hours from *trans*-1,2-diaminocyclohexane, the sulfonyl chloride, and triethyl amine.[2] Bissulfonamides **1a - c** can be generated more conveniently in high yield and purity employing the tartrate salt of the resolved *trans*-1,2-diaminocyclohexane.[3] This route circumvents the need for isolation of the resolved free diamine, which is tedious due to its high solubility in water and its air-sensitivity.

The key step in the synthesis of the ligands outlined in Scheme 1 involves a directed ortho metallation reaction of the bissulfonamides **1a - c** with *n*-BuLi.[4,5] It is known that sulfonamides of primary amines, which are deprotonated under the reaction conditions to give sulfonamidos, are excellent directing groups in ortho metallations. The sulfonamido is a more effective directing group than the methoxy group and is comparable to aromatic amides.[6]

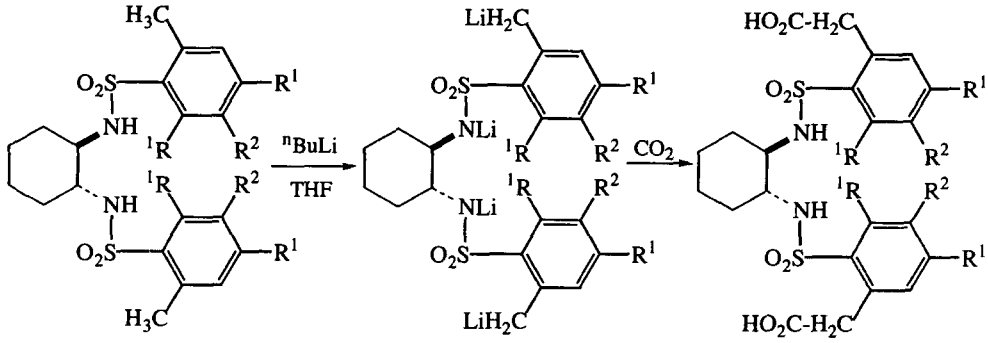
The tetradentate ligands **3 - 6** are synthesized from the bissulfonamide complexes according to Scheme 1. Addition of 5 equivalents of *n*-BuLi to a THF solution of the bissulfonamides **1a** and **1b** at 0 °C results in formation of the tetralithium derivatives **2a** and **2b**. These intermediates can be quenched with CO_2 to provide the diacids **3a** and **3b**. Treatment of the reaction mixture with saturated aqueous $NaHCO_3$ followed by acidification and extraction into ethyl acetate provides the ligands along with the by-product pentanoic acid. Recrystallization of this mixture from THF / hexanes gave yields of 67 and 56 % for **3a** and **3b** respectively.

Ketones which do not contain alpha hydrogens also have proven to be reliable electrophiles for this procedure. Thus, the ortholithiated derivatives **2a - c** can be quenched with benzophenone, 9-fluorenone or hexafluoroacetone to give diol ligands **4a, 4b, 4c, 5b** and **6b** in 60, 71, 82, 55 and 65 % respectively, after purification by column chromatography on silica.

It has been shown that substrates with alkyl substituents ortho to the directing group undergo lateral lithiations over ortho metallation.[7,8] We have observed parallel reactivity with the bissulfonamide ligands. Reaction of **7** and **8** (Scheme 2) with 5 equivalents of *n*-BuLi resulted in directed lithiation of the ortho methyl group giving the metallated derivative **9** which was quenched with CO_2 as described above. The resulting diacids **10** and **11** were formed in 47 and 51 % recrystallized yield respectively. Resonances for the diastereotopic hydrogens alpha to the carboxylic acid are clearly observed between 3.9 and 4.3 ppm (J = 17 Hz) by ^1H NMR spectrometry.

As part of our research program, we are interested in the application of chiral sulfonamide based ligands.[9] Due to the strongly electron withdrawing nature of the sulfonyl group, the sulfonamide N-H is acidic, having pKa's similar to phenols. Furthermore, the deprotonated sulfonamide is a poor electron donor relative to metal amides ($M\text{-}NR_2$) and the resulting sulfonamido complexes are strong Lewis acids. Several of these chiral sulfonamido complexes have been successfully applied to asymmetric catalysis. Ideally, the new tetradentate ligands described herein will create a more rigid environment around the metal center, thus simplifying determination of the reactive conformation of the catalyst and facilitating rational modification of the metal-ligand system.

Scheme 2



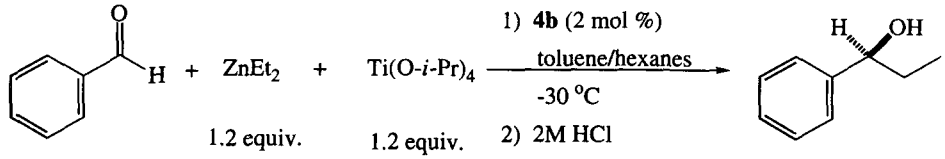
7, $R^1 = CH_3$, $R^2 = H$
8, $R^1 = H$, $R^2 = CH_3$

9

10, $R^1 = CH_3$, $R^2 = H$
11, $R^1 = H$, $R^2 = CH_3$

Preliminary results indicate that the bissulfonamide / diol based ligands readily bind to titanium and are efficient asymmetric Lewis acid catalysts. We chose the asymmetric addition of alkyl groups to aldehydes to evaluate the performance of complexes derived from these ligands. It has been established that bissulfonamides are excellent ligands[2,9] for this ligand accelerated process.[10] Employing ligand **4b** under standard conditions (as outlined in Equation 1) resulted in the production of (R)-1-phenyl-1-propanol in high ee and yield. This encouraging result suggests that these ligands may be of general use in asymmetric Lewis acid catalysis.

Equation 1



92 % ee, 90 % yield

In summary, we have developed an efficient method to synthesize tetradentate sulfonamide based ligands. We are currently exploring the structure / enantioselectivity relationship of complexes derived from these ligands and evaluating their use in asymmetric catalysis.

Acknowledgments

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5. Sample Procedure, Synthesis of **4b**: The reaction was conducted under a nitrogen atmosphere. The bissulfonamide **1b** (1.03 g, 2.44 mmol) was placed in a flask equipped with a side arm, a magnetic stirring bar and 20 mL of THF (which had been dried over sodium/benzophenone). The reaction mixture was cooled to 0 °C and *n*-BuLi (5.3 mL 2.3 M, 12.2 mmol, 5 eq.) was added dropwise. As the *n*-BuLi was added, the solution became clear yellow. The reaction was stirred for 20 min at 0 °C and benzophenone (1.55 g, 8.54 mmol, 3.5 eq.) was added as a solid. The reaction was stirred for 30 min at 0 °C followed by an additional hour at room temperature. The solvent was removed under reduced pressure and the resulting solid treated with 20 mL of 1 M $NaHSO_4$ and 30 mL of ethyl acetate. The aqueous layer was extracted two more times with 20 mL of ethyl acetate. The organic layers were combined, dried and the solvent removed under reduced pressure. The remaining solid was chromatographed using silica and 20 % ethyl acetate/80 % hexanes. The final product was obtained as a white solid (1.37 g,1.74 mmol, 71 %). Data for **4b**: mp 105-109° C; ^1H NMR ($CDCl_3$, 200 MHz) d 8.05 (d, J = 8.2 Hz, 2H), 7.30 (m, 13H), 7.21 (m, 11H), 6.64 (s, 2H), 5.90 (s, 2H), 4.68 (s, 2H), 2.95 (s, 2H), 2.30 (s, 6H), 1.67 (d, J=13.31 Hz, 2H), 1.40 (s, 2H), 1.06 (s, 2H), 0.90 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 60 MHz) d 146.6, 146.2, 145.2, 142.2, 137.0, 133.7, 131.4, 128.6, 128.1, 128.1, 128.0, 127.9, 127.6, 127.5, 82.9, 56.2, 32.0, 23.4, 21.5; IR (KBr) 3420.4, 3056, 2962, 2865, 1488, 1396, 1323, 1274, 1047, 904, 760, 702 cm^{-1}. Data for **3b**: mp = 111-113 °C; ^1H NMR ($CDCl_3$, 200 MHz) d 8.98 (s, 2H); 7.95 (d, J = 8.0 Hz, 2H); 7.73 (d, J = 1.5 Hz, 2H); 7.44 (dd, J = 8.0, J = 1.5 Hz, 2H), 5.30 (s, 2H), 3.05 (s, 2H); 2.43 (s, 6H); 1.89 (m, 2H), 1.48 (m, 4H); 1.05 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 60MHz) d: 170.7, 143.6, 137.0, 132.7, 132.4, 129.8, 129.5, 56.8, 23.7, 21.2, 21.0 ppm. IR (KBr): 3271, 3178, 2922, 1722, 1411, 1333, 1250, 1161, 1117, 1050, 944, 900, 833, 750, 700, 600, 556 cm^{-1}.
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