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A Simple and Efficient Synthetic Route to Enantiopure Scorpionate Ligands

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A simple and efficient synthetic route for the preparation of enantiopure scorpionate ligands is described that allows the optimization and rapid access to ligands with diverse chiral environments.

Introduction

The traditional approach to asymmetric catalysis with metal-based catalysts is an iterative operation that revolves around the synthesis of chiral ligands of high enantiopurity.[1] Once the chiral ligands have been bound to the metal centers, the new catalysts are examined to determine their enantioselectivities and activities. The results of these studies are evaluated, and the next generation of ligands is designed. In this process, the key to efficient reaction optimization is often rapid access to numerous catalysts with diverse chiral environments. Unfortunately, the synthesis of enantiopure ligands can be an arduous task, severely hampering the optimization of the asymmetric process.[2]

During the last decade, our research group has been interested in the synthesis of new "heteroscorpionate" ligands[3] with pyrazole rings. These new ligands are related to the tris(pyrazol-1-yl)methane system,[4] but in this case one of the pyrazole groups is replaced by a carboxylate, dithiocarboxylate, methoxy, or cyclopentadienyl[5] group. We recently reported a racemic example of a bis(pyrazol-1-yl)acetate tripod ligand in which the chirality originates from the two different pyrazolyl donor groups bound to the methoxyacetate moiety.[6] More recently, Burzlaff et al.[7] prepared two enantiopure NNO acetate–scorpionate ligands in which the chirality originates from pyrazolyl groups; the process involved three synthetic steps. We present here a simple, versatile, and efficient synthetic route for the preparation of enantiopure scorpionate ligands in one step by an insertion reaction of a commercial, enantiopure isocyanate or isothiocyanate into a conventional bis(pyrazol-1-yl)methane. This approach extends our method for the insertion of carbon dioxide into the bridging carbon atom to other types of heterocumulenes. We have prepared the first amidate and thioamidate lithium compounds as a new class of enantiopure scorpionate ligands. These ligand systems can be optimized by modifications in both the bis(pyrazol-1-yl)methane and the isocyanate or isothiocyanate moieties to give diverse chiral environments. Titanium complexes have been prepared with these types of chiral ligands.

Results and Discussion

Deprotonation at the methylene group of bis(3,5-dimethylpyrazol-1-yl)methane (bdmpzm)[8] with *n*BuLi, followed by reaction with achiral and chiral isocyanates [e.g., *tert*-butyl isocyanate and (*S*)-(–)-α-methylbenzyl isocyanate] and isothiocyanates [e.g., *tert*-butyl isothiocyanate and (*S*)-(–)-1-phenylpropyl isothiocyanate] yielded the lithium compounds $[Li(tbpam)]_2$ (**1**) [tbpam = *N*-*tert*-butyl-2,2-bis(3,5-dimethylpyrazol-1-yl)acetamidate], $[Li(S\text{-}mbbpam)]_2$ (**2**) [S-mbbpam = (*S*)-(–)-*N*-α-methylbenzyl-2,2-bis(3,5-dimethylpyrazol-1-yl)acetamidate], $[Li(tbptam)]_2$ (**3**) [tbptam = *N*-*tert*-butyl-2,2-bis(3,5-dimethylpyrazol-1-yl)thioacetamidate], and $[Li(S\text{-}ppbptam)]_2$ (**4**) [S-ppbptam = (*S*)-(–)-*N*-1-phenylpropyl-2,2-bis(3,5-dimethylpyrazol-1-yl)thioacetamidate], which were isolated as white or yellow solids in good yield (85%) after the appropriate work-up (see Scheme 1).

The mass spectra (FAB) of **1**–**4** indicate a dinuclear formulation. The ^1H and $^{13}C\text{-}\{H\}$ NMR spectra of **1** and **3** (achiral compounds) show a single set of resonances for the pyrazole rings, indicating that the two pyrazole rings are equivalent. However, the ^1H and $^{13}C\text{-}\{H\}$ NMR spectra of complexes **2** and **4** (chiral compounds) exhibit two resonances for each of the H^4, Me^3, and Me^5 pyrazole protons, indicating that the two pyrazole rings are nonequivalent.

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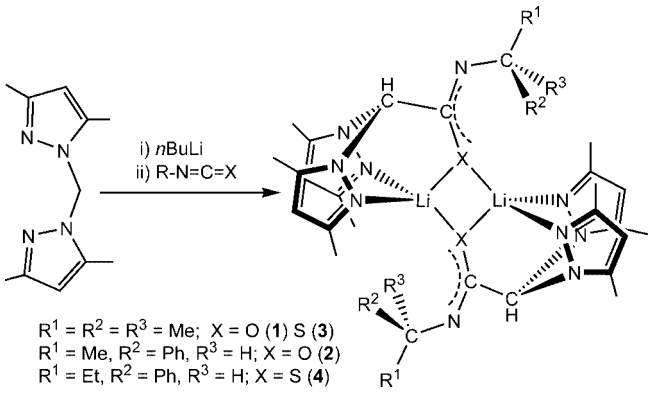


Scheme 1. Synthesis of lithium compounds **1**–**4**.

These results agree with a proposed tetrahedral arrangement for the lithium atoms with a κ^3-NNE-coordination (E = O or S) for the heteroscorpionate ligand, where the oxygen or the sulfur atom of the scorpionate ligands bridge the two lithium atoms (see Scheme 1). In this arrangement, when $R^1 = R^2 = R^3$ (achiral compounds), there is a symmetry plane that contains the lithium atoms, the bridging carbon atoms of the pyrazolyl rings, and the amidate or thioamidate fragments. However, when $R^1 \neq R^2 \neq R^3$, this symmetry plane does not exist, and the pyrazole rings are nonequivalent. This structural arrangement was corroborated by an X-ray crystal structure determination for **1** (see Figure 1).[9] The geometry around the Li atom can be described as a distorted tetrahedron with a "heteroscorpionate" ligand that acts in a tridentate fashion (two coordinated pyrazole rings and an oxygen atom from the amidate fragment bridge the lithium atoms). The dimeric aggregate is based on Li_2O_2 four-membered rings, which have previously been observed in other lithium compounds containing, for example, anionic tris(imidazol-2-yl)phosphanes,[10] boroxides,[11] aryloxides,[12] or ester enolate[13] ligands. However, it should be noted that compounds with this type of metallacycle containing a scorpionate ligand have not been reported in the literature. The corresponding Li–O bond lengths are essentially the same as in the lithium compounds mentioned above, although notable asymmetry is present within the amidate bridge [Li(1)–O(1) = 1.946(8) Å; Li(1)–O(2) = 1.825(8) Å; Li(2)–O(1) = 1.860(8) Å; Li(2)–O(2) = 1.978(7) Å]. Thus, the four-membered ring is approximately a square that is slightly folded about the Li···Li and O···O diagonal (21.0° and 24.4°, respectively), the Li···Li diagonal being much shorter than the O···O diagonal.

The C(12)–O(1) and C(12)–N(5) bond lengths [1.290(5) and 1.287(5) Å] or C(28)–O(2) and C(28)–N(10) bond lengths [1.291(5) and 1.271(5) Å] indicate the existence of a delocalized O–C–N bond in both amidate fragments of the heteroscorpionate ligands, which presents a Z-geometry for the C=N bonds. The absence of a response in the ^{1}H NOESY-1D experiment from the *tert*-butyl group upon irradiating the methyne bringing group confirms this geometry in solution. In the chiral complexes **2** and **4**, we confirmed the presence of one enantiomer in solution by the addition of a chiral shift reagent, namely (*R*)-(–)-(9-anthryl)-2,2,2-trifluoroethanol. The addition of this compound did not modify the ^{1}H NMR spectra of either compound. However, addition of the shift reagent to a racemic mixture of complex **2** gave rise to the appearance of two signals for each proton in the ^{1}H NMR spectra, resulting from the two diastereoisomers of the corresponding two enantiomers. In addition, the specific rotations of **2** and **4** were examined by optical polarimetry. Preliminary studies also show that this type of isocyanate and isothiocyanate can be inserted into other types of bis(pyrazol-1-yl)methane.

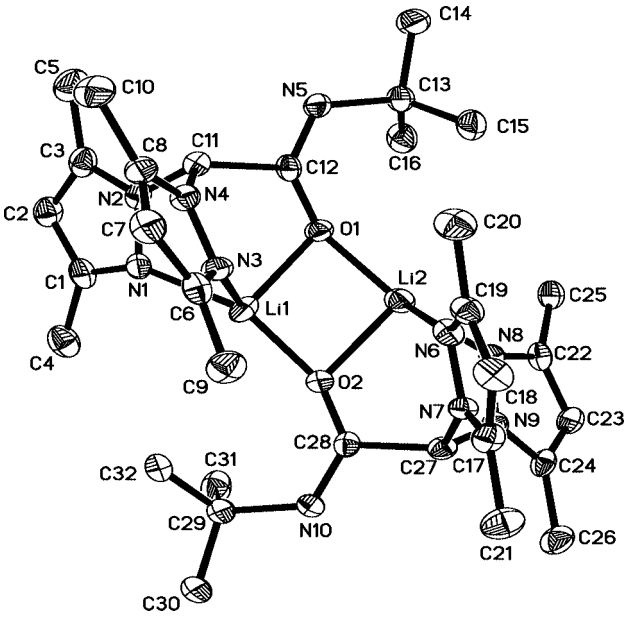
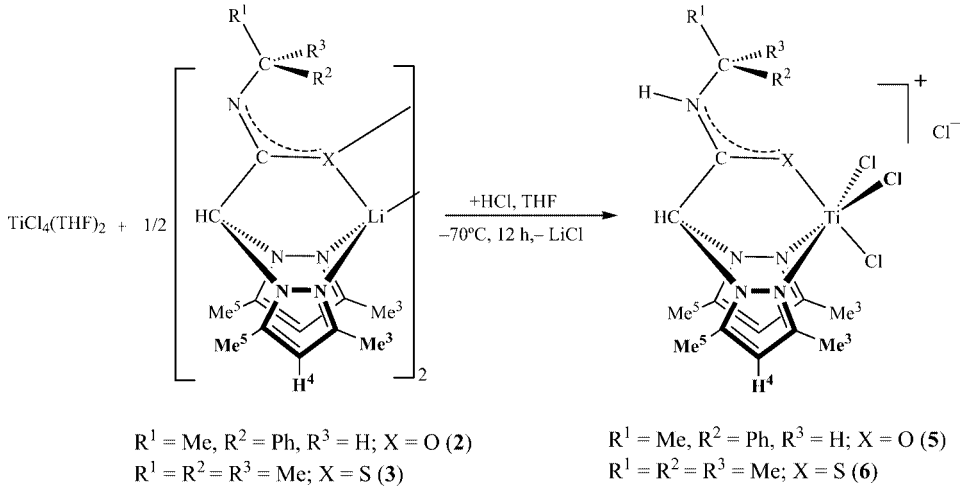


Figure 1. ORTEP diagram of **1** with 30% probability ellipsoids. Selected bond lengths [Å] and angles [°]: Li(1)–O(1), 1.946(8); Li(1)–O(2), 1.825(8); Li(2)–O(1), 1.860(8); Li(2)–O(2), 1.978(7); Li(1)–N(1), 2.063(8); Li(1)–N(3), 2.017(8); C(12)–O(1), 1.290(5); C(12)–N(5), 1.287(5); C(28)–O(2), 1.291(5); C(28)–N(10), 1.271(5); O(1)–Li(1)–O(2), 98.5(4); Li(1)–O(1)–Li(2), 80.4(3); O(1)–Li(2)–O(2), 96.1(3); Li(1)–O(2)–Li(2), 80.5(3).

These lithium compounds have been used for the synthesis of new titanium complexes. Thus, **2** and **3** reacted with $[TiCl_4(THF)_2]$ to give the complexes $[TiCl_3$(S-mbbpamH)]Cl (**5**) [S-mbbpamH = (*S*)-(–)-*N*-α-methylbenzyl-2,2-bis(3,5-dimethylpyrazol-1-yl)acetamide] and $[TiCl_3$(tbptamH)]Cl (**6**) [tbptamH = *N*-*tert*-butyl-2,2-bis(3,5-dimethylpyrazol-1-yl)thioacetamide] (see Scheme 2). Although the reactions were carried out under rigorously anhydrous experimental conditions, the presence of adventitious HCl proceeding from $TiCl_4$ in the reaction mixture during the work-up procedure was probably responsible for the protonation of the acetamidate or thioacetamide moieties and their transformation into carboxamide[14] or thiocarboxamide moieties, respectively. However, the character of the enantiopure scorpionate ligand in complex **5** is not modified. The ^{1}H and ^{13}C{H}-NMR spectra of **5** and **6** exhibit two singlets and one singlet, respectively for each of the H^4, Me^3 and Me^5 pyrazole protons. An X-ray crystal structure analysis was carried out for complex **6** (see Figure 2).[9] The titanium



Scheme 2. Synthesis of titanium complexes **5** and **6**.

center has a distorted octahedral environment with a major distortion in the N(3)–Ti(1)–Cl(2) angle, which has a value of 166.1(2)°. In addition, the specific rotation of **5** was examined by optical polarimetry.

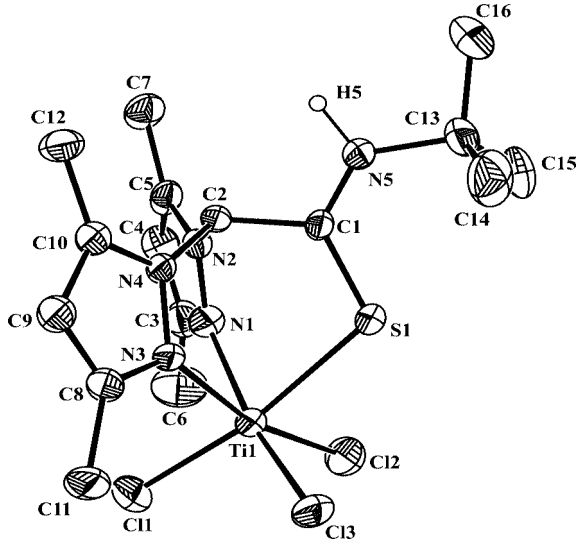


Figure 2. ORTEP diagram of **6** with 30% probability ellipsoids. Selected bond lengths (Å) and angles [°]: Ti(1)–N(3), 2.144(7); Ti(1)–N(1), 2.192(7); Ti(1)–Cl(3), 2.217(3); Ti(1)–Cl(1), 2.231(3); Ti(1)–Cl(2), 2.243(3); Ti(1)–S(1), 2.500(3); S(1)–C(1), 1.672(8); N(5)–C(1), 1.31(1); N(3)–Ti(1)–Cl(2), 166.1(2); N(1)–Ti(1)–Cl(3), 167.1(2); Cl(1)–Ti(1)–S(1), 170.5(1); N(5)–C(1)–S(1), 126.3(6).

In conclusion, we present here a simple and efficient synthetic route for the preparation of enantiopure scorpionate ligands. This approach will allow the optimization and rapid access to numerous ligands with diverse chiral environments by modification of the bis(pyrazol-1-yl)methane as well as the enantiopure isocyanate and isothiocyanate fragments. In addition, these lithium compounds are excellent reagents for the introduction of these ligands into transition-metal complexes.

Experimental Section

All reactions were performed using standard Schlenk-tube techniques under dry nitrogen. Solvents were distilled from appropriate drying agents and degassed before use. Microanalyses were carried out with a Perkin–Elmer 2400 CHN analyzer. Mass spectra were recorded with a VG Autospec instrument using the FAB technique and nitrobenzyl alcohol as matrix. ^{1}H- and ^{13}C NMR spectra were recorded with a Varian Inova FT-500 spectrometer and referenced to the residual deuterated solvent. Optical rotations were determined with a Perkin–Elmer 241 MC polarimeter at the sodium D line, equipped with a quartz cell of 1.00-dm path length. Experimental procedures and characterization data for compounds **1**–**6** are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Spectroscopic data and experimental procedures for compounds **1**–**6**.

Acknowledgments

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[9] Crystallographic data for **1**: $C_{32}H_{48}Li_2N_{10}O_2$·THF, orthorhombic, $P2_12_12_1$, a = 11.567(1), b = 17.538 (1), c = 19.568 (1) Å; V = 3969.7 (5) Å^3; Z = 4; $D_{calcd.}$ = 1.156 g/cm^3; λ (Mo-K_α) = 0.71073 Å; μ (Mo-K_α) = 0.075 mm^{-1}; 100(2) K; R = 0.0447; R_w = 0.1134. Crystallographic data for **6**: $[C_{16}H_{25}Cl_3N_5STi]$-Cl·0.5CH_2Cl_2·0.25C_6H_{14}, monoclinic, $C2/c$, a = 37.375(5), b = 9.892 (3), c = 30.905 (3) Å; V = 11326 (4) Å^3; Z = 16; $D_{calcd.}$ = 1.345 g/cm^3; λ (Mo-K_α) = 0.71073 Å; μ(Mo-K_α) = 0.862 mm^{-1}; 230(2) K; R = 0.0839, R_w = 0.2532. The R factors obtained are high because of the poor quality of the crystals. CCDC-277594 (**1**) and CCDC-277595 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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