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Highly Diastereoselective Nucleophilic Addition to Myrtenal. Straightforward Synthesis of an Enantiopure Scorpionate Ligand

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The work described here represents the first example in which an efficient and highly diastereoselective nucleophilic 1,2-addition of an organolithium reagent has been performed on a carbonylic prostereogenic center to give an enantiopure scorpionate ligand in only one step.

One of our research areas concerns the synthesis of enantiopure "heteroscorpionates"[1] bearing pyrazole rings.[2] One of the most important and fundamental synthetic procedures to establish stereoselectively a new C−C bond is the enantioselective 1,2-addition of organometallic reagents to aldehydes to afford chiral secondary alcohols.[3] This fact led us to focus our attention on (1*R*)-(−)-myrtenal as a possible chiral substrate to control the stereochemistry of a newly created asymmetric center. Zepeda et al.[4] recently reported the synthesis of myrtenal derivatives and assessed them as chiral auxiliaries in nucleophilic additions of Grignard reagents or organolithiums. Furthermore, myrtenal has been employed in several processes involving 1,2-addition of organometallics to aldehydes, namely, in the synthesis of polymetallic macrocyclic terpene-derived hybrids,[5] in the stereoselective preparation of polycyclic cyanohydrins,[6] in the synthesis of unsaturated nitriles,[7] and in the allylation of aldehydes with allenes.[8] We present here an efficient and highly diastereoselective one-pot preparation of an enantiopure scorpionate ligand[9] by means of a 1,2-addition of a lithium bis(pyrazol-1-yl)methane derivative to (1*R*)-(−)-myrtenal. This approach extends our method for the preparation of heteroscorpionates[10] to other types of substrates. Additionally, we tested the potential utility of this process in enantioselective syntheses; for example, enantiopure titanium complexes were also prepared and characterized.

A cold (−10 °C) tetrahydrofuran (THF) solution of lithium bis(3,5-dimethylpyrazol-1-yl)methide,[10] prepared in situ from Bu^{n}Li and bis(3,5-dimethylpyrazol-1-yl)methane (bdmpzm)[11] at −70 °C, was added dropwise to a THF solution containing 1 equiv of the commercially available (1*R*)-(−)-myrtenal, and this addition gave rise to a rapid color change from yellow to colorless. After 5 min, the reaction was complete

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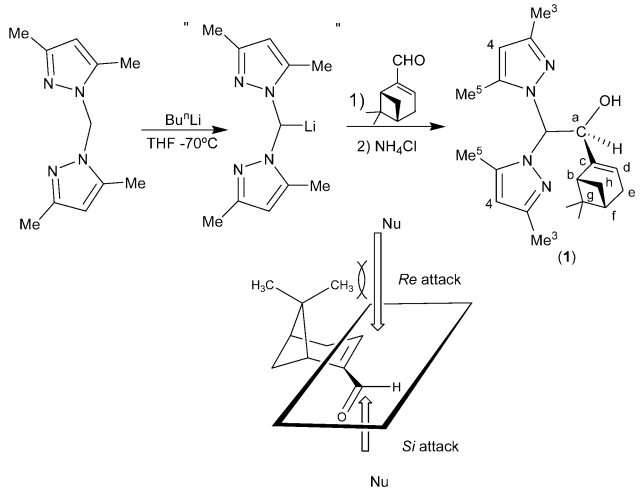
Scheme 1. Synthesis of Enantiopure Heteroscorpionate Ligand (*R*,*R*)-bpzmmH (**1**)



and the appropriate workup gave the enantiopure heteroscorpionate compound (*R*,*R*)-bpzmmH {**1**; (*R*,*R*)-bpzmmH = (1*R*)-1-[(1*R*)-6,6-dimethylbicyclo[3.1.1]2-hepten-2-yl]-2,2-bis(3,5-dimethylpyrazol-1-yl)ethanol} as a white solid in good yield (83%) and with an excellent diastereomeric excess (>99% de; Scheme 1).[12] This procedure constitutes an efficient and highly diastereoselective method to prepare enantiopure scorpionate ligands in a one-pot process. Initial evidence for the stereochemical route was obtained from the X-ray molecular structure of **1** (Figure 1), which shows the *R* configuration for the newly formed chiral center (see below), denoting that the diastereofacial attack of the nucleophile had proceeded through the *Si* face of the carbonyl group in an s-trans conformation. The steric effects from the methyl groups of the bicycle moiety are probably the main driving force for the observed diastereoselectivity in the process (Scheme 1).

This diastereoselectivity was assessed by considering the ^{1}H NMR spectrum and integrating the CH^a or Me signals of the bicycle in the crude reaction mixture because the chemical shifts of these protons appear systematically at higher field for the *S* epimer. A diastereomeric ratio denoted as ">99:1" signifies that only the major diastereoisomer was detected. The ^{1}H NMR spectrum of **1** exhibits two singlets for each of the H^4, Me^3, and Me^5 pyrazole protons, indicating that the two pyrazole rings are inequivalent, and a doublet at 4.36 ppm, which corresponds to the O−H group. As mentioned above, the absolute configuration of **1** was verified by single-crystal X-ray diffraction analysis (Figure 1)[13] to have the *R* configuration at C^a (C12 and C33). The pyrazole rings of this compound are oriented in a quasi-antiparallel manner with respect to each other, presumably to minimize the intramolecular steric interaction between the N2 and N4 atoms of the two rings. This conformation is similar to that found with the (2-hydroxyphenyl)bis(pyrazolyl)methane[14] and 1,1′-[2-(1,3-cyclopentadien-2-yl)-2-phenylethylidene]bis-

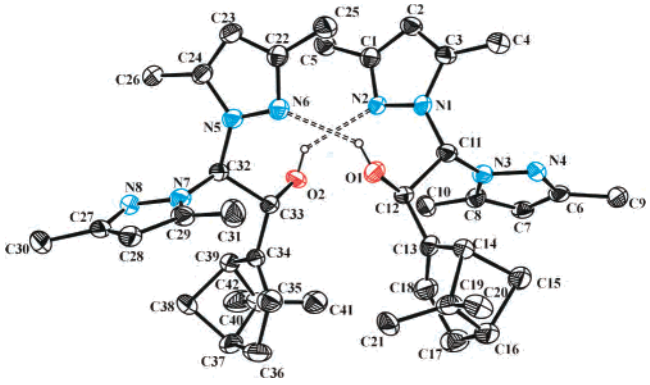


Figure 1. ORTEP diagram of **1** with 30% probability ellipsoids. Selected bond lengths (Å) and angles (deg): N1−C11 1.457(8), N3−C11 1.468(8), C11−C12 1.555(8), O1−C12 1.460(8), O2−C33 1.434(8); N1−C11−N3 110.0(6), O1−C12−C11 104.9(6), O1−C12−C13 105.9(7), O2−C33−C34 106.3(7), O2−C33−C32 106.6(6), N5−C32−C33 109.7(6).

(3,5-dimethylpyrazole)[15] derivatives. A symmetry expansion of the asymmetric unit reveals that each molecule is intermolecularly hydrogen-bonded to one adjacent molecule in the crystal lattice through the alcohol O−H (O1 or O2) groups of one molecule and the N6 or N2 pyrazoles of the other one, respectively. This gives rise to dimeric species through hydrogen bonding [O1···N6 and O2···N2 separations: 2.896(8) and 2.884(7) Å, respectively]. The methyl groups of the bicycle system within each molecule are oriented approximately perpendicular and point outward to the *cis*-pyrazole ring, probably to minimize steric interactions between these two units.

Having prepared this new enantiopure heteroscorpionate ligand in the form of the alcohol, we explored its potential utility as a tridentate ligand in the preparation of chiral group 4 metal complexes. Deprotonation of the alcohol group of **1** with NaH, followed by reaction with $TiCl_4$ in a 1:1 molar ratio, yielded the enantiopure titanium complex [$TiCl_3$[(*R*,*R*)-bpzmm]] {**2**; (*R*,*R*)-bpzmm = (1*R*)-1-[(1*R*)-6,6-dimethylbicyclo[3.1.1]2-hepten-2-yl]-2,2-bis(3,5-dimethylpyrazol-1-yl)ethoxide}, which was isolated as a yellow solid. In addition, the treatment of a THF solution of Ti(NMe$_2$)$_4$ with **1** afforded the enantiopure triamido derivative [Ti(NMe$_2$)$_3$-[(*R*,*R*)-bpzmm]] (**3**) as an orange solid (Scheme 2).

The ^{1}H NMR spectra of complexes **2** and **3** show two singlets for each of the H^4, Me^3, and Me^5 pyrazole protons, one singlet for each of the methine groups (CH bridge of pyrazole rings and CH^a) and two singlets for the methyl groups, four multiplets for protons H^b, H^d, H^e, and H^f, and

(12) The synthesis of a chiral pyrazolylpyridine-based *N*,*N*,*O*-scorpionate ligand through a non-stereoselective nucleophilic addition to a ketone has recently been reported: Gennari, M.; Tegoni, M.; Lanfranchi, M.; Pellinghelli, M. A.; Marchiò, L. *Inorg. Chem.* **2007**, *46*, 3367.

(13) Crystallographic data for **1**: $C_{21}H_{30}N_4O$, monoclinic $P2_1$, a = 11.516(2) Å, b = 13.671(3) Å, c = 13.296(3) Å, β = 99.851(9)°, V = 2062.3(7) Å^3, Z = 4, D_{calc} = 1.142 g/cm^3; λ(Mo Kα) = 0.710 73 Å, μ(Mo Kα) = 0.072 mm^{-1}; T = 180(2) K; X8 APEX II CCD diffractometer, graphite monochromator, 7223 unique reflections. R = 0.0634; R_w = 0.1260. Crystal diffracted weakly. The compound crystallizes with two molecules of **1** per asymmetric unit. Crystallographic data for **2**: $C_{21}H_{29}Cl_3N_4Ti$, orthorhombic, $P2_12_12_1$, a = 10.667(2) Å, b = 13.303(2) Å, c = 17.080(3) Å, V = 2423.8(6) Å^3, Z = 4, D_{calc} = 1.391 g/cm^3, λ(Mo Kα) = 0.710 73 Å, μ(Mo Kα) = 0.704 mm^{-1}, T = 180(2) K; X8 APEX II CCD diffractometer, graphite monochromator, 9910 unique reflections. R = 0.0474; R_w = 0.0970.

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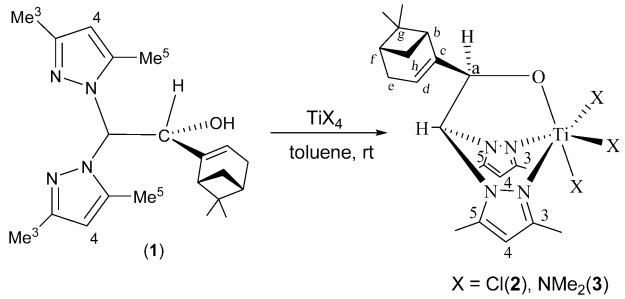
Scheme 2. Synthesis of the Titanium Complexes $[TiX_3[(R,R)\text{-bpzmm}]]$[a]



[a] (**2**): (i) NaH, (ii) $TiCl_4$. (**3**): (iii) $Ti(NMe_2)_4$.

two multiplets for the geminal-H^h bicycle protons. The 1D ^1H NOESY NMR experiments permitted the univocal assignment of all ^1H NMR resonances. These results are consistent with an octahedral structure resulting from the κ^3-NNO coordination of the ligand to the metal center (Scheme 2).

Crystals of **2** were grown from a dichloromethane solution. The molecular structure determined by X-ray diffraction (Figure 2)[13] is in good agreement with the solution structure proposed on the basis of NMR experiments. The titanium has a distorted octahedral geometry in which the heteroscorpionate ligand is coordinated by the two nitrogen atoms of the pyrazole rings and the oxygen atom of the alkoxide group, and three chlorine atoms occupy the other three sites of the octahedron. The scorpionate ligand maintains the *R* configuration for the C^a (C12) atom. The Ti−Cl1 and

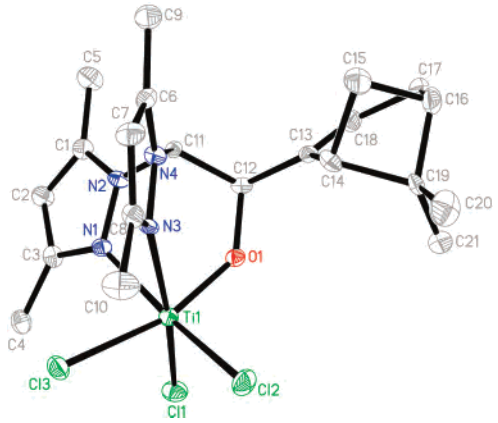


Figure 2. ORTEP diagram of **2** with 30% probability ellipsoids. Selected bond lengths (Å) and angles (deg): Ti1−O1 1.802(4), Ti1−N1 2.206(6), Ti1−N3 2.210(5), Ti1−Cl2 2.255(2), Ti1−Cl1 2.289(2), Ti1−Cl3 2.323(2); O1−Ti1−N1 81.64(19), O1−Ti1−Cl2 96.56(14), O1−Ti1−Cl3 163.98(16).

Ti−Cl2 bond lengths of 2.289(2) and 2.255(2) Å, respectively, are shorter than that of Ti−Cl3 [2.323(2) Å]; the former values are very similar to those observed in the octahedral structure of the hydridotris(pyrazol-1-yl)boratetitanium trichloride complex,[16] where the chlorine atoms are trans to the pyrazolyl nitrogen atoms. The lengthening of the Ti−Cl3 bond was ascribed to a trans influence of the alkoxide oxygen atom.

It is worth noting the close proximity of the stereogenic carbon C^a to the metal, an arrangement that is able to create an effective chiral pocket around the Ti center. This characteristic may be very useful in subsequent studies on its reactivity in enantioselective processes.

Thus, in a preliminary study, it has been found that the reaction of **3** with $SiMe_3Cl$ in a 1:2 molar ratio gave rise to the isolation of only one of the three possible diastereoisomers of the enantiopure chloro−amidotitanium complex $[TiCl_2(NMe_2)[(R,R)\text{-bpzmm}]]$ (**4**), revealing that, in fact, chiral induction from the ligand to the titanium center took place.

In conclusion, we present here a one-pot synthetic procedure for an enantiopure scorpionate ligand through a highly diastereoselective nucleophilic 1,2-addition of a lithium bis(pyrazol-1-yl)methane derivative to (1*R*)-(−)-myrtenal. This synthetic approach should be amenable to providing rapid access to a wide variety of ligands with diverse chiral environments by modification of the bis(pyrazol-1-yl)methane. In addition, this compound has proven to be an excellent reagent to introduce chirality into transition-metal complexes, a fact confirmed by reaction with both titanium halide and amide.

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Supporting Information Available: X-ray crystallographic data in CIF format and synthesis, spectroscopic data, and details of data collection, refinement, atom coordinates, anisotropic displacement parameters, and bond lengths and angles for these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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