COMMUNICATION

Synthesis of an Enantiopure Scorpionate Ligand by a Nucleophilic Addition to a Ketenimine and a Zinc Initiator for the Isoselective ROP of *rac*-Lactide

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A novel nucleophilic addition of an organolithium to a ketenimine to prepare an enantiopure NNN-heteroscorpionate ligand is described. We verified its potential utility as a valuable scafford for chirality induction through the preparation of enantiopure zinc complexes, which behave as highly efficient initiators to produce highly-enriched isotactic poly(lactide)s (P_i up to 0.88).

During the last decade our research group has contributed widely to the design of new enantiopure "heteroscorpionate" ligands,[1] related to the bis(pyrazol-1-yl)methane system,[2] to prepare efficient catalysts[3] for the well-controlled ROP of cyclic esters such as *rac*-LA. Thus, we have prepared new chiral NNO,[4] NNN[5] and NNCp[6] scorpionate ligands in a single high-yielding step by an enantioselective nucleophilic addition of an organolithium to an aldehyde (C=O), imine (C=N) and fulvene (C=C), respectively. In these derivatives, the chiral substrate to control the stereochemistry of the newly created asymmetric center[7] was in one carbon of the double bond, not in a donor atom. Expectedly, when these ligands were transferred onto a metal to prepare an enantiopure scorpionate complex, this new stereogenic center remained too far from the metal. Therefore, when these complexes were used as initiators for the ring-opening polymerization (ROP) of lactides,[3,6] the remoteness of the chiral substrate could influence (negatively) in the isotactic enrichment of the resulting poly(lactide)s (PLAs) through an enantiomorphic-site control mechanism. With this aim in mind, we focused now our attention on enantiopure ketenimine compounds,[8] where the stereogenic center is in the N-donor atom, and it is not necessary an "enantioselective" nucleophilic addition of organolithium compound to generate an enantiopure heteroscorpionate ligand. Ketenimines are a class of nitrogenated cumulenes, where their C=C=N heterocumulenic system contains a central *sp*-hybridized carbon atom, which is decisive to confer high reactivity in this class of organic compounds, since this carbon is electron-deficient and could be attacked by nucleophiles. In general, successful cyclization involves additions of nucleophiles to ketenimines,[9] also they are known, for example, reactions with nucleophiles such as amines, alcohols, or water to give amidines, imidates or amides respectively.[10] However, the addition of organolithium compounds have not been published yet. Therefore, we present here the first nucleophilic addition of an organolithium to a ketenimine as a simple and efficient synthetic route that allowed us to isolate an enantiopure NNN-donor heteroscorpionate ligand. This compound contains the chiral substrate in the N-donor atom. This ligand has been subsequently transferred onto Zn(II) to give an enantiopure scorpionate-zinc complex where the sterogenic center is near to the metal. The zinc complex was assessed as initiator for the stereoselective ring-opening polymerization of *rac*-lactide.

Singer and Lee[8a] prepared in the 70's the first ketenimines with the asymmetric center directly attached to the nitrogen atom ($Ph_2C{=}C{=}NCR_1R_2R_3$). These compounds were prepared by reaction of the triphenylphosphinalkylimine with diphenylketene (aza-Wittig method of synthesis)[11]. Following this method of reaction, we have prepared a new enatiopure ketenimine (**2**), which was obtained as an orange oil in good yield (ca. 90%) (Scheme 1) by reaction of the same ketene and a new enatiopure phosphanimine (**1**) prepared with phenylphosphine dibromide[8] and the commercially available (-)-*cis*-Myrtanylamine (Scheme 1). The ^{1}H NMR spectra of **1** and **2** (Figures S1 and S2 in the ESI†) show the corresponding signals for the phenyl groups of phosphanimine or ketenimine. In addition, the spectra exhibit a multiplet for the methylene group and the signals corresponding to the bicyclic fragment (six sets of resonances for H^b, H^c, H^d, H^e, H^f and *geminal*-H^h, and two singlets for the methyl groups). ^{1}H-^{13}C heteronuclear correlation (g-HSQC) experiments allowed us to assign the resonances corresponding to the ^{13}C{^{1}H} NMR spectra of these compounds.

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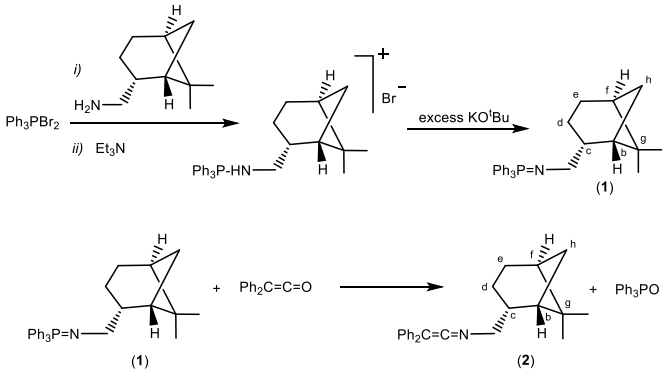
† Electronic Supplementary Information (ESI) available: Figures, tables, text, and a CIF files giving details of the synthesis and spectroscopic data for all compound details of data collection, refinement, atom coordinates, anisotropic displacement parameters, and bond lengths and angles for **5**, and details of the ring-opening polymerization of *rac*-lactide with complexes **4** and **5**. CCDC 1915940. See DOI: 10.1039/x0xx00000x

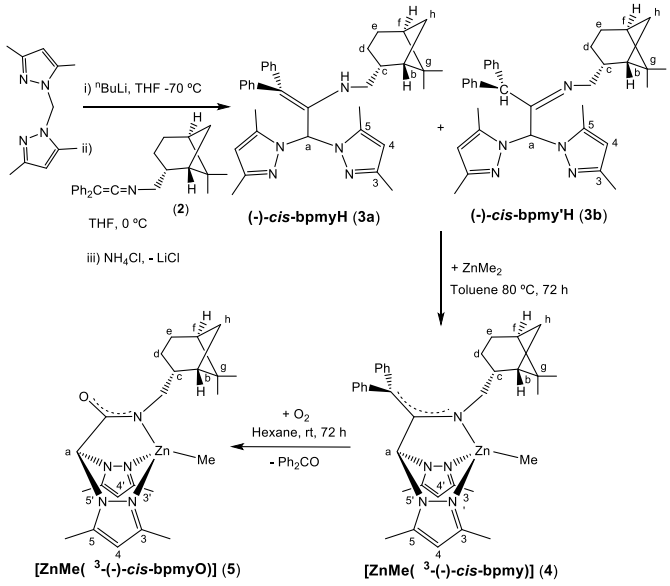


Scheme 1. Synthesis of enantiopure phosphanimine **1** and ketenimine **2**.

Once the new optically active ketenimine (**2**) was synthesized, we focused our attention on the second step, i.e., the preparation of enantiopure scorpionate ligands using the novel reaction based on the nucleophilic addition of organolithium reagents to ketenimines. Thus, a cold (0 ºC) THF solution of lithium bis(3,5-dimethylpyrazol-1-yl)methanide,[12] prepared *in situ* from ^{n}BuLi and bis(3,5-dimethylpyrazol-1-yl)methane (bdmpzm) at –70 ºC, was added dropwise to a THF solution containing 1 equiv of the new ketenimine (**2**). The addition gave rise to a rapid colour change from orange to yellow. The reaction was complete after 1h and the appropriate work-up gave a 1:1 mixture of the two enantiopure heteroscorpionate tautomers (amine or imine derivative), (-)-*cis*-bpmyH (**3a**) {bpmyH = 3,3-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-1,1-diphenylprop-1-en-2-amine and (-)-*cis*-bpmy'H (**3b**) {bpmy'H = (*Z*)-1,1-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-3,3-diphenylpropan-2-imine} as yellow solids, in 68% yield (Scheme 2). Both tautomers can be separated by crystallization.

The ^{1}H NMR spectrum of **3** (Figure S3 in the ESI†) exhibits four singlets for each of the H^{4}, Me^{3} and Me^{5} pyrazole protons, indicating the presence of two tautomers and the inequivalence of the two pyrazole rings. The spectrum also contains two singlets for the CH^{a} bridge to the two pyrazole rings and two multiplets for the methylene group. Two set of signals for the phenyl groups and the bicycle moiety were also observed for both tautomers. In compound **3a** the signal corresponding to the N-H group can be observed, while in the **3b** it disappears and a new signal corresponding to the proton $CHPh_2$ is observed.

Having prepared this new enantiopure heteroscorpionate ligand in the form of the amine or imine, in a further step, we explored its potential utility as a tridentate ligand in the preparation of enantiopure zinc metal complexes. Deprotonation of **3** with $ZnMe_2$ in a 1:1 molar ratio yielded the enantiopure zinc complex [ZnMe(κ^3-(-)-*cis*-bpmy)] (**4**), which was isolated as an orange solid in excellent yield (93%) (Scheme 2). When a hexane solution concentrated of **4** was slowly evaporated at room temperature in an air atmosphere, pale orange crystals were deposited from the solution after 72 h, and these were identified by an X-ray crystal structure determination as the enantiopure zinc complex [ZnMe(κ^3-(-)-*cis*-bpmyO)] (**5**) [bpmyO



Scheme 2. Synthesis of enantiopure heteroscorpionate ligand (**3**) and the zinc complexes (**4** and **5**).

= 2,2-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-*N*-(((1*S*,2*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)acetamide (Scheme 2).

The formation of **5** may be the final result of the oxidative cleavage of the enamine double bond. This type of reaction has been known for a long time,[13] and a number of different reagents have been developed to achieve the transformation, mainly, sodium periodate,[14] sodium dichromate in acid,[15] or molecular oxygen with copper ion systems.[16] However, as far as we know, zinc-catalyzed oxygenation of enamines has not been described in the literature. We believe that the oxidation that takes place here is probably catalyzed by the presence of the metal center (zinc), since this process was not observed in compound **3** under otherwise identical conditions. In the mother liquor of the crystallization solution, we have been able to observe by ^{1}H NMR the presence of diphenyl ketone. Attempts to crystallize complex **4** in an inert atmosphere and in different solvent mixtures resulted fruitless.

The ^{1}H NMR spectrum of complexes **4** and **5** (Figures S4 and S5 in the ESI†) show two singlets for each of the H^{4}, Me^{3} and Me^{5} pyrazole protons, one singlet for the CH^{a} bridge, one multiplet for methylene group, and one set of signals for the phenyl groups and the bicycle for the complex **4**. However, complex **5** does not present the set of signals corresponding to the phenyl groups. In both complexes, we can observe a singlet corresponding to the methyl group coordinated to zinc around zero ppm. The ^{1}H NOESY-1D experiments allowed the unequivocal assignment of all ^{1}H resonances and ^{1}H-^{13}C heteronuclear correlations (g-HSQC) the ^{13}C{^{1}H} NMR spectra.

The structure of **5** was verified by single crystal X-ray diffraction analysis (Figure 1, selected bond lengths and angles as well as crystallographic details are collected in the experimental Section in the ESI†). The scorpionate ligand retains the enantiopure configuration in the complex. In addition, the specific rotation of all compounds was examined by optical

polarimetry (see Experimental Section in the ESI†). The zinc atom has a distorted tetrahedral geometry in which the

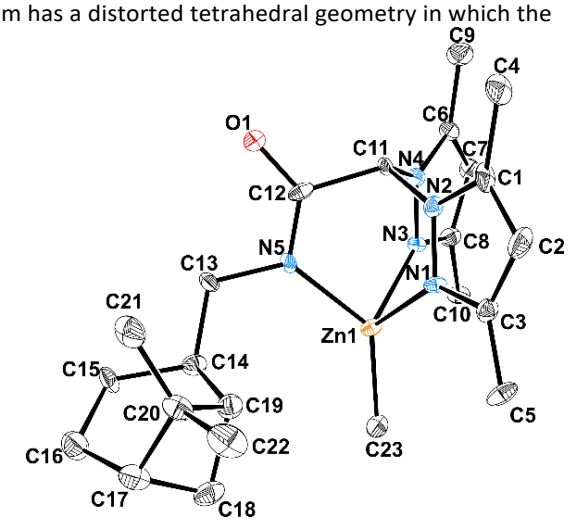


Figure 1. ORTEP diagram of **5** with 30% probability ellipsoids. Selected bond lengths (Å) and angles (deg): Zn(1)−N(5) 1.986(10); Zn(1)−N(1) 2.117(9); Zn(1)−N(3) 2.122(10); Zn(1)−C(23) = 1.962(13); O(1)−C(12) = 1.235(14) Å, C(12)−N(5) = 1.325(15) Å.

heteroscorpionate ligand acts in a tridentate fashion and is coordinated by the two nitrogens of the pyrazole rings and the nitrogen atom of amide group, with the Zn-methyl group occupying the fourth site of the tetrahedron. The N(1)–Zn and N(3)–Zn bond lengths [2.117(9) Å and 2.122(10) Å] compare well with that observed in other NNO-heteroscorpionate zinc alkyls,[17] but are considerably longer than the N(5)–Zn bond length [1.986(10) Å]. The Zn–C(23) bond length [1.962(13) Å] can be regarded as normal considering the distances reported for analogs zinc alkyls.[17] Finally, partial delocalization in the acetamidate O(1)−C(12)−N(5) core is also observed [O(1)−C(12) = 1.235(14) Å, C(12)−N(5) = 1.325(15) Å], a common behaviour in related families of monomeric organoderivatives.[18]

The final stage was to inspect the potential utility of this new enantiomerically pure zinc complex as a valuable initiator for the ring-opening polymerization (ROP) of *rac*-lactide (*rac*-LA), capable to exert remarkable levels of isotacticity through an enantiomorphic site control mechanism. In this context, given the biocompatibility[19] of this metal, several zinc-based catalysts have been successfully employed in the stereocontrolled ROP of *rac*-LA for the production of highly-enriched isotactic PLAs,[6,20] which afford an interesting wide array of applications (packaging, microelectronics and biomedical).[21]

As a result, we preliminarily assessed the catalytic activity of the zinc alkyl (**4**) in the ROP process of *rac*-LA under different conditions.

The experimental M_n values of the PLAs produced showed good agreement with the expected theoretical values [$M_{n(calcd)}PLA_{100}$ = 14 400 g·mol^{-1}] (Table S1 in the ESI†). Inspection of the size exclusion chromatography (SEC) data for the resulting polyesters showed a monomodal weight distribution, with dispersity values ranging from 1.07 to 1.22 (Figure S6 in the ESI†), suggesting well-controlled living propagations and the existence of a single type of reaction site.

Thus, **4** acted as an efficient single-component initiator and 37% of *rac*-LA was transformed at 50 ºC after 2.5 h in tetrahydrofuran, with low molecular weight PLA materials and narrow polydispersity values obtained (Table S1 in the ESI†, entry 1; M_n = 4 900, M_w/M_n = 1.07). The analog alkyl **5** resulted similarly active, and 34% of the monomer was converted after 2.5 h at 50 ºC, with similar features in the materials produced and slight increase in the dispersity value (Table S1 in the ESI†, entry 6). After 10 h, almost complete conversion was reached for **4**. The use of toluene as solvent as well as decrease on temperature reaction led to a dramatic decrease in the catalytic activity, as only traces were obtained in both cases. MALDI-ToF MS (Figure S7 in the ESI†) of low molecular weight materials evidenced an initial addition of the methyl fragment to the monomer. More interestingly, microstructural analysis of the poly(*rac*-lactide) revealed that initiators **4** and **5** exert a remarkable preference for isotactic dyad enchainment, reaching P_i values of 0.87-0.88, (Figures 2 and S8 and Table S2 in the ESI†), values that parallel the highest achieved for the very scarce zinc catalysts bearing chiral ancillary ligands, which have already succeeded in the isoselective ROP of *rac*-LA (P_i = 0.91,[20a] 0.84,[20b,c] 0.92[20d] 0.89[20e]), and much higher than our previously communicated NNCp-scorpionate alkyl zinc initiator (P_i = 0.77).[6] Additionally, inspection of the tetrads resulting from stereoerrors (*i.e.*, tetrads other than *iii*) suggested that an enantiomorphic site control mechanism[22] is dominant ([*sis*]/[*sii*]/[*iis*]/[*isi*] = 1/1/1/2 ratio, Figure S8 and Table S2 in the ESI†). This behavior for catalyst **4** is most probably the result of the high level of homosteric control caused by the accurate architecture of this novel enantiomerically pure NNN-scorpionate ligand.

Conclusions and Perspectives

In conclusion, we present here the preparation of a new enantiopure NNN-donor heteroscorpionate ligand containing the chiral substrate in the N-donor atom. This ligand has been synthetized trough a nucleophilic addition of an organolithium to an enatiomerically pure ketenimine, which is the first example of this type of reaction. In addition, this compound proved to be an excellent reagent to introduce chirality in metal complexes, a fact confirmed by reaction with dimethylzinc. These enantiopure NNN-heteroscorpionate methyl zinc complexes act as efficient initiators for the ROP of *rac*-LA, exerting a high homosteric control in the production of highly-enriched isotactic poly(lactide)s (P_i up to 0.88) from *rac*-LA.

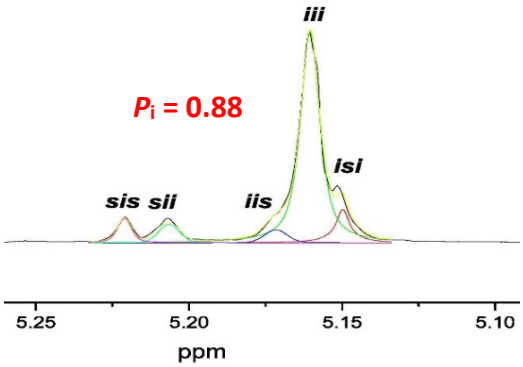


Figure 2. Deconvoluted ^{1}H NMR spectra (500 MHz, 298 K, $CDCl_3$) of the homodecoupled C*H* resonance of poly(*rac*-lactide) prepared employing [ZnMe(κ^3-(-)-*cis*-bpmy)] (**4**) as initiator in tetrahydrofuran at 50 ºC for 2.5 h.

Further work is on progress in our laboratories to extend the great potential of this promising enantiomerically pure ligand for the preparation of new and distinct polymers with enhanced enantioselectivity from conventional monomers through rational tuning on the ligand design.

Conflicts of interest

There are no conflicts to declare.

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