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A general and efficient method for the preparation of unsymmetrical bidentate P,N and P,S ligands

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Abstract—A general and efficient preparation of chiral and achiral P,N and P,S ligands is described where ligands are prepared by reacting a variety of 2- or α-lithio *N*- or *S*-heterocycles and a lithiated phosphine with 1,2-cyclic sulfates.

The search for new ligands for homogeneous catalysis is a field of continuing interest. A huge effort has been devoted to the development of highly efficient transition metal catalyzed reactions using ligands based on P–P, P–N, or N–N coordination modes.[1] Of special interest are the P,N ligands due to their unsymmetrical nature.[2] The ligand imparts bonding versatility and enables tuning of the electronic and steric properties of the donor atoms. This heterofunctional system can display unique dynamic features, such as hemilability, which represents an efficient way to control the selectivity of catalytic processes.[3] These features of P,N ligands are useful in homogeneous transition metal catalysis for C–C bond forming reactions such as oligomerization, polymerization, and copolymerization of olefins.[4] In addition to this, chiral P,N ligands are useful in asymmetric catalysis.[5] For example, oxazole based chiral P,N ligands are now widely used in various asymmetric reactions and these can be considered as privileged ligands.[5,6] Due to the importance and growing demand of P,N ligands, their easy accessibility is highly desirable. We report here a simple, and generic one-pot reaction that affords a variety of chiral/achiral P,N and P,S ligands containing various *N*- and *S*-heterocycles.

In this route we used 1,2-cyclic sulfates as starting materials, since these are easily accessible by the Sharpless protocol in which diols are treated with $SOCl_2$ to form cyclic sulfites, which are then oxidized to cyclic sulfates with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$.[7] Cyclic sulfates readily undergo mono substitution reactions at the ring carbon with a range of nitrogen, oxygen, sulfur, and carbon based nucleophiles.[8,9] Double substitution reactions with dianions leading to the loss of sulfate have also been reported.[10] Inspired by this, we envisaged that it would be possible to attach an appropriate heterocyclic ring and a phosphine moiety to the two different ring carbons of a 1,2-cyclic sulfate to afford a hetero bidentate phosphine ligand.[11] To initiate our studies, we first chose a simple symmetric cyclic sulfate **1** to produce imidazole-based P,N ligands **2a** and **2b** according to Scheme 1.

First, the cyclic sulfate **1** was treated with an equimolar amount of the 2-lithio *N*-heterocycle in THF at −78 °C resulting in quantitative ring opening of the five-membered ring. Addition of the second nucleophile, $LiPPh_2$, led to the displacement of the sulfate group by the PPh_2 moiety. Subsequent hydrolysis and work-up afforded the crude ligand **2a** as a viscous liquid and **2b** as white powder. The hydrobromide salt of **2b** (oxide) was obtained when **2b** was treated with an equimolar amount of 47% HBr in ethanol for 2 h. A good quality crystal suitable for X-ray analyses was obtained from its ethanol-diethyl ether solution. The molecular structure of **2b** (oxide)·HBr·C_2H_5OH is depicted in Figure 1.[12]

The satisfactory result obtained from the successive addition of two different nucleophiles led us to investigate the reactions of non-symmetrical 1,2-cyclic sulfates.

Keywords: P,N Ligands; P,S Ligands; Cyclic sulfates; Imidazole; Asymmetric synthesis.
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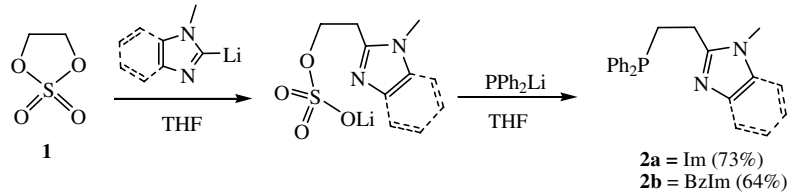


Scheme 1. Synthesis of ligands **2a** and **2b** using the symmetric cyclic sulfate **1**.

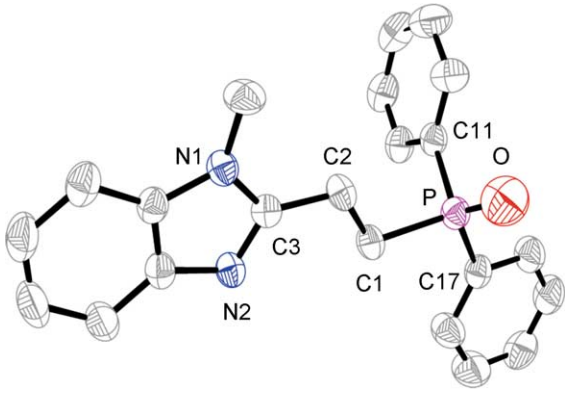


Figure 1. Molecular structure of **2b** (oxide)·HBr·C_2H_5OH. Selected bond lengths [Å] and bond angles [°]: P–C1 1.808(4), P–C11 1.812(4), P–Cl7 1.808(4), P–O 1.396(5); C1–P–C11 101.81(17), C1–P–Cl7 105.27(17), C11–P–C17 103.66(17), P–C1–C2 109.5(2), Cl–C2–C3 114.1(3). All hydrogen atoms, the bromide ion, and the solvent molecule are omitted for clarity.

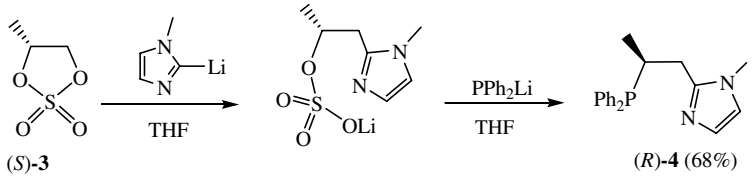
We conducted reactions using the cyclic sulfate **3** in its racemic and non-racemic forms. Successive addition of 2-lithio *N*-methylimidazole and $LiPPh_2$ to **3** in an analogous way to that described for **2** led to the formation of the ligand **4** in 68% yield (Scheme 2).

Starting from the *S* enantiomer **3**, (*R*)-**4** was obtained stereoselectively through inversion of the configuration at the stereogenic center. The reaction was highly regioselective with the first *C*-nucleophile attacking the less hindered carbon atom of the cyclic sulfate exclusively, as was evidenced by the coupling of the methyl protons with the phosphorus atom. The methyl protons of **4** appeared at $\delta = 1.04$, as a doublet of doublets, with a coupling constant $^3J_{PH} = 15.0$ Hz.

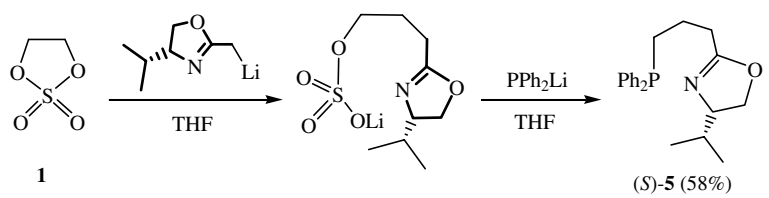
Encouraged by this result, we decided to attach an optically active heterocyclic moiety to this ligand system and to this end, successfully constructed the ligand **5** containing an oxazole ring according to Scheme 3.

The chiral oxazole used in this reaction was readily prepared from L-valinol by reacting with ethyl iminoacetate hydrochloride.[13] Several convenient routes are available for the construction of similar types of chiral oxazoles with different substituents at the 5-position, and this broadens the scope for the preparation of a series of chiral oxazoline ligands.[14] Recently Gilbertson et al. synthesized a series of similar ligands by multi-step reactions where the oxazole and phosphine moieties were connected by two carbon atoms and these ligands were successfully utilized in palladium-catalyzed allylic alkylations reactions.[15] Very high ee (90–97%) and conversions were achieved, in some cases, for the alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.

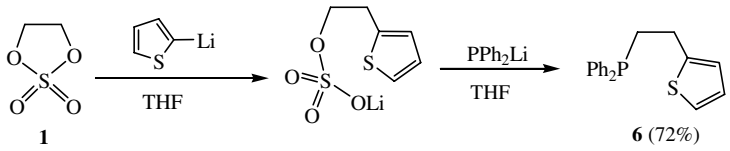
To explore the wider application of this methodology, we also prepared a representative P,S ligand **6** by attaching the sulfur-containing heterocycle, thiophene, according to Scheme 4. Recently P,S ligands have been shown to be very effective in asymmetric catalytic reactions.[16] Therefore, the scope of this protocol is wide as various heterocycles can be attached to this system.



Scheme 2. Synthesis of ligand **4** using the unsymmetric cyclic sulfate **3**.



Scheme 3. Synthesis of ligand (*S*)-**5** having a chiral center in the heterocyclic ring.



Scheme 4. Synthesis of ligand **6** containing a *S*-heterocycle.

In conclusion, we have reported a simple reaction for the preparation of a variety of P,N and P,S ligands containing various *N*- and *S*-heterocycles. The synthetic strategy can be extended to other heterocyclic-phosphine ligands. The procedure allows the steric and electronic properties of ligands to be fine tuned by choosing different cyclic sulfates and by changing the substituents on the phosphorus or the heterocyclic ring.

Acknowledgments

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Supplementary data

Supplementary data (synthetic and spectroscopic data for the compounds **2a**–**b**, **4**, **5**, and **6**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.041.

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