Asymmetric 1,3-dipolar cycloaddition with a *P*-stereogenic dipolarophile: An efficient approach to novel *P*-stereogenic 1,2-diphosphine systems†

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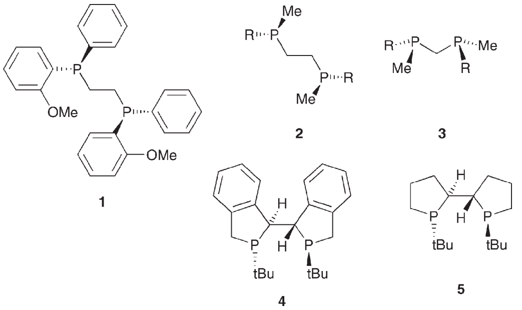
The asymmetric 1,3-dipolar cycloaddition of the *P*-stereogenic dipolarophile (S_P,S_P)-6 to *C*,*N*-diphenylnitrone (7) led to previously unknown *P*-stereogenic isoxazolinyl diphosphine dioxides (R_P,S_P)-8 in *enantio*- and diastereomerically pure form; their stereospecific reduction with Ti(OiPr)$_4$/PMHS proceeds in high yield with retention of configuration at the phosphorus atoms to give *enantio*- and diastereomerically pure diphosphines, which are conveniently purified *via* the corresponding diphosphine-diboranes.

Asymmetric catalysis has been the most challenging and highly rewarding field in organic chemistry for the last decades.[1,2] Within the area of transition metal catalysis chiral ligands, in particular phosphines,[3] have gained prime importance.

Nowadays, asymmetric catalysis using optically active diphosphine ligands is an important field of synthetic organic chemistry.[4] Optically active diphosphines possessing chiral centers at the phosphorus atoms rather than in the carbon backbone have become increasingly important not only in stereochemical studies of organophosphorus compounds but also as chiral ligands in transition metal catalyzed asymmetric reactions.[5–9] Diphosphines with two stereogenic phosphorus atoms such as DIPAMP (**1**) are often catalytically more active than the corresponding *P*-stereogenic monophosphines.[10–14]

Recently, Imamoto[15–22] and Zhang[23–28] developed highly efficient *P*-stereogenic bidentate ligands such as **2–5**, which were successfully used in the asymmetric hydrogenation of various prochiral substrates with high degrees of enantioselectivity (Scheme 1). However, approaches to *P*-stereogenic diphosphanes with additional chiral centers in the molecular backbone still remain rare.[29–31]

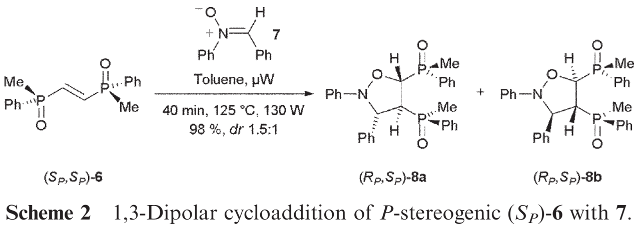


Scheme 1 *P*-stereogenic diphosphine ligands (R = alkyl, aryl).

Recently, we demonstrated that the homo-metathesis of (S_P)-methylphenylvinylphosphine oxide[32] in the presence of modern olefin metathesis precatalysts allows the efficient synthesis of *P*-homochiral (S_P,S_P)-**6**.[33–35] Here we report the stereoselective 1,3-dipolar cycloaddition of (S_P,S_P)-**6** and *C*,*N*-diphenylnitrone (**7**) as part of the synthesis of a new *P*-stereogenic diphosphine ligand. The use of alkenylphosphorus compounds as dipolarophiles for 1,3-dipolar cycloaddition reaction is still limited to few examples.[36–39] The 1,3-dipolar cycloaddition with nitrones produces isoxazolidines with the additional possibility of a subsequent hydrogenolysis of the N–O bond. Therefore these heterocycles deserve interest as precursors for the respective amino alcohols.

P-stereogenic diphosphine dioxide (S_P,S_P)-**6** was treated with *C*,*N*-diphenylnitrone (**7**) in boiling benzene for 2 d. The ^{31}P NMR spectrum of the crude reaction mixture showed two doublets for **8a** at δ = 38.0 (d) and at 39.8 (d) ppm, those of **8b** appear at δ = 36.1 (d) and at 37.8 (d) ppm. The two products formed in the ratio of 1.5 : 1 are diastereomers (R_P,S_P)-**8a** and (R_P,S_P)-**8b**, which were easily separated by column chromatography (Scheme 2). This 1,3-dipolar cycloaddition can also be performed under microwave irradiation. With toluene as the solvent it was possible to significantly reduce the reaction time from 2 d to 40 min without decrease of the yield, no alteration in diastereoselectivity was observed.

Since 1,3-dipolar cycloaddition reactions are known to proceed with complete stereospecificity, it was rational to conclude the *trans* arrangement of the phosphorous



Scheme 2 1,3-Dipolar cycloaddition of *P*-stereogenic (S_P)-**6** with **7**.

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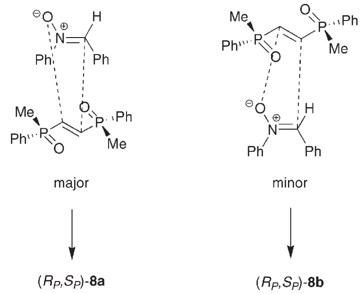


Scheme 3 Proposed transition states for the formation (R_P,S_P)-**8a** (major) and (R_P,S_P)-**8b** (minor).

substituents at the isoxazolidine ring. NOE measurements confirmed the *all-trans* configurations of all substituents at the isoxazolidine rings in (R_P,S_P)-**8a** and in (R_P,S_P)-**8b** (see ESI).†

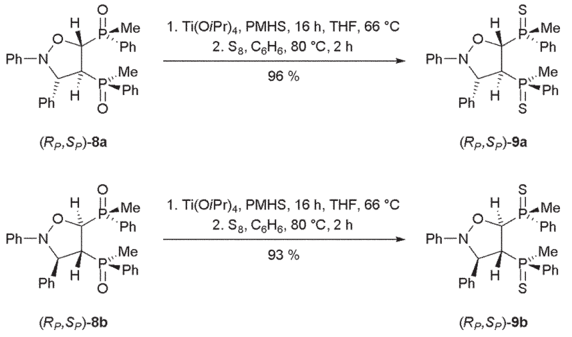
Each of the cycloadducts contains five centers of chirality with the configurations at the phosphorus atoms pre-determined by that given in (S_P,S_P)-**6**. Application of the CIP rules to cycloadducts **8** changes the priorities at the phosphorus atom next to the isoxazolidine oxygen atom as compared to (S_P,S_P)-**6** resulting in (R_P,S_P) configurations in **8a** and **8b**. Taking the *trans* configuration of (S_P,S_P)-**6** into account, four diastereomeric cycloadducts had to be expected, two of which were formed. These show a *trans* configuration between the phenyl substituent at the isoxazolidine ring and the phosphorus substituent next to it.

While **7** has two enantiotopic faces, (S_P,S_P)-**6** has two diastereotopic faces. Assuming a *s-cis,s-cis* conformation of (S_P,S_P)-**6**[37,39–44] the transition states leading to the major diastereomer (R_P,S_P)-**8a** and to the minor diastereomer (R_P,S_P)-**8b** are characterized by an attack of **7** with its *Re* face or its *Si* face, respectively, at (S_P,S_P)-**6** in a way that the nitrone C-phenyl and the dipolarophile P substituents end up as *trans* in the cycloadducts. The preference of the formation of (R_P,S_P)-**8a** as compared to that of (R_P,S_P)-**8b** may be explained by the different steric bulk of the phenyl *vs.* methyl substituents at phosphorus pointing to the nitrone in the transition states (Scheme 3).

The stereospecific reduction of *P*-stereogenic phosphine oxides to *P*-stereogenic phosphines with *retention* or *inversion* of configuration has been developed,[5] however, applications to *P*-stereogenic diphosphines are still rare. For such reductions low reaction temperatures have to be maintained in order to avoid racemization of the phosphines caused by thermally induced inversion.[45–47]

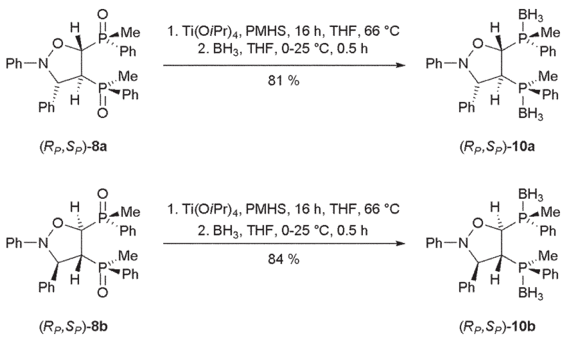
Unfortunately, the use of the common silane reagents such as $PhSiH_3$ or $HSiCl_3/Et_3N$ in the reduction of (R_P,S_P)-**8a** resulted in partial or complete racemization at phosphorus as indicated by ^{31}P NMR. However, finally *P*-stereogenic diphosphine dioxide (R_P,S_P)-**8a** and (R_P,S_P)-**8a** were stereospecifically reduced in the presence of Ti(O*i*Pr)$_4$ and polymethylhydrosiloxane (PMHS)[48,49] to give the corresponding diphosphines, which were subsequently treated with elemental sulfur to give diastereomerically pure diphosphine disulfide (S_P,R_P)-**9a** or (S_P,R_P)-**9b** in 96 and 93% yield, respectively (Scheme 4).

It is well known that *P*-stereogenic phosphine-boranes are stable precursors to *P*-stereogenic phosphines, which can easily be handled in the air and purified by column chromatography without decomposition.[5,9,50,51] Consequently, treatment of the above crude reduction mixtures with $BH_3 \cdot THF$ resulted in the formation of diastereomerically pure diphosphine diboranes (S_P,R_P)-**10a** and (S_P,R_P)-**10b** in 81 and 84% yield, respectively (Scheme 5).



Scheme 4 Stereospecific reduction of diphosphine dioxides (*Rp*,*Sp*)-**8a** and (*Rp*,*Sp*)-**8a**.

On the basis of the determined crystal structure (Fig. 1) it was possible to assign the absolute configuration of all the stereogenic centers in (S_P,R_P)-**10b**. The absolute configurations of the phosphorus atoms are *S* (P1 at C5) and *R* (P2 at C4). The absolute configurations of the carbon atoms in the isoxazolidine ring are *R* (C3), *R* (C4), and *S* (C5). This assignment is fully in accord with NOE based assignments of the relative configuration in the diastereomeric diphosphine dioxides (R_P,S_P)-**8a** and (R_P,S_P)-**8b**. Regarding the absolute configuration of the starting diphosphine dioxide (R_P,S_P)-**8b** it can be concluded that the reduction proceeded with *retention* of configuration at both phosphorus



Scheme 5 Formation of borane adducts (S_P,R_P)-**10a** and (S_P,R_P)-**10b**.

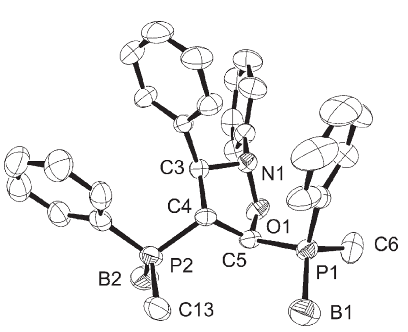
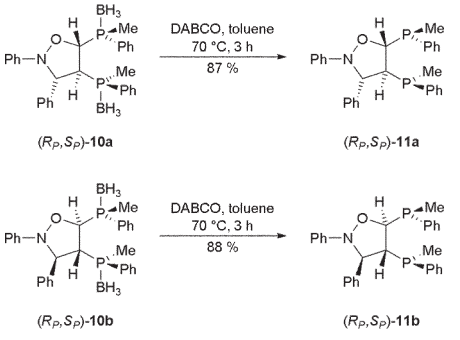


Fig. 1 Structure of minor (S_P,R_P)-**10b** in the crystal (there exist two crystallographically independent molecules both of which possess the same configuration but differ slightly in the conformation; only one molecule is shown; see ESI†).[52]



Scheme 6 Synthesis of *P*-stereogenic diphosphines (S_P,R_P)-**11a** and (S_P,R_P)-**11b**.

atoms leading to *P*-stereogenic diphosphine with absolute configuration S_P (P1) and R_P (P2).

A *P*-stereogenic phosphine-borane is usually treated with an excess of amine to give after filtration the pure phosphine with complete retention of configuration at phosphorus.[9,50,51] Reaction of the P-stereogenic diphosphine diboranes (S_P,R_P)-**10a** and (S_P,R_P)-**10b** with 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene led to *P*-stereogenic diphosphines (S_P,R_P)-**11a** and (S_P,R_P)-**11b** in 87 and 88% yield, respectively, which were virtually pure according to their ^{1}H, ^{13}C, ^{31}P NMR spectra (Scheme 6).

In conclusion, we have developed an approach to novel *C*,*P*-stereogenic diphosphines by asymmetric 1,3-dipolar cycloaddition and stereospecific reduction reaction sequence. Asymmetric catalysis based on these novel *C*,*P*-chiral ligands is underway in our laboratories.

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