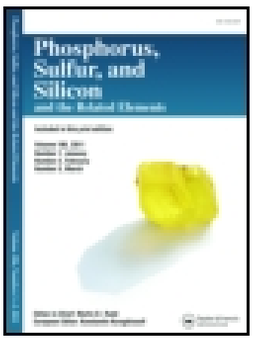

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Novel 1,3,2-diazaphospholidines with pseudodipeptide substituents

I. V. Chuchelkin[a], V. K. Gavrilov[a], I. D. Firsin[a], V. S. Zimarev[a], I. M. Novikov[a], M. G. Maksimova[a], A. A. Shiryaev[a], S. V. Zheglov[a], V. A. Tafeenko[b], V. V. Chernyshev[b], and K. N. Gavrilov[a]

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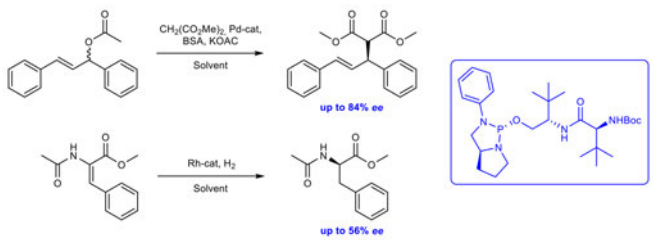
ABSTRACT

Chiral 1,3,2-diazaphospholidine with pseudodipeptide substituents was prepared. This asymmetric inducer provided up to 84% ee in the Pd-catalyzed asymmetric allylic alkylation of (E)-1,3-diphenylallyl acetate with dimethyl malonate, and up to 53% ee in the Rh-catalyzed asymmetric hydrogenation of (Z)-methyl 2-acetamido-3-phenylacrylate.

GRAPHICAL ABSTRACT



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Chiral 1,3,2-diazaphospholidine; pseudodipeptide; Pd-catalyzed asymmetric allylation; Rh-catalyzed asymmetric hydrogenation

1. Introduction

Asymmetric metal complex catalysis is an efficient tool for the synthesis of enantiopure and, in general, enantioenriched organic and organoelement compounds. Such products are used in the preparation of pharmaceutical drugs, vitamins, chemical plant-protecting agents, perfume compounds, and food additives, as well as ferroelectric liquid crystals and chiral polymers with nonlinear optical properties. The activity and stereoselectivity of metal complex catalysts is governed to a considerable degree by an adequate strategy for the design and synthesis of corresponding chiral ligands, primarily, phosphorus-containing ones thousands representatives of which have been used in various asymmetric transformations.[1–5]

Among numerous phosphorus-containing stereo inducers, phosphite-type ligands are of particular interest. They are characterized by the oxidative stability, considerable π-acidity, ease of preparation by simple condensation (including techniques of parallel and solid-phase synthesis), and a low cost. These key benefits allow one to build up a wide library of ligands and to select the most efficient asymmetric inducers for each catalytic process.[4–7]

Very attractive are diamidophosphites, which, on the one hand, have balanced electronic properties and involvement of the phosphorus atom into the 1,3,2-diazophospholidine cycle increases oxidation and hydrolytic stability of the ligand. On the other hand, the possibility to widely vary the phosphorus and/or nitrogen substituents allows the fine-tuning of its steric and electronic properties.[8–12] The presence of an asymmetric donor phosphorus atom significantly facilitates the chirality transfer from the chiral catalyst to the product.[13–16]

It should be noted that the presence of the pseudodipeptide fragments in the phosphorus containing stereo inducers structure makes it possible to form supramolecular assemblies based on them, in which two ligands are bound by hydrogen bonds. Currently, there are examples of successive application of supramolecular systems based on porphyrin and amide derivatives in the asymmetric metal complex catalysis.[17–23]

This work describes the preparation of a chiral diamidophosphite based on a pseudodipeptide bearing a stereogenic phosphorus atom in the 1,3,2-diazophospholidine cycle and its application in the enantioselective Pd-catalyzed allylic substitution and Rh-catalyzed hydrogenation reactions. Such reactions are widely used for estimation of the catalytic performance of new chiral inducers and for asymmetric synthesis of valuable organic and natural compounds.[1 , 6, 13, 15, 24–32]

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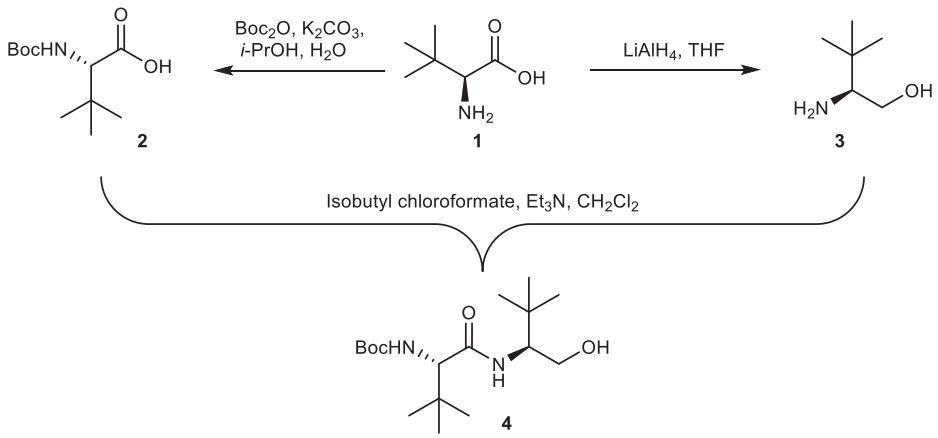
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/gpss.



Scheme 1. Synthesis of the pseudodipeptide 4.

2. Results and discussion

2.1. Synthesis of organic compounds

The compound **4** was obtained by a three-step synthesis from (*S*)-*tert*-leucine **1** using optimized known techniques:[33] the *N*-Boc (*S*)-derivative **2** was synthesized by the reaction (*S*)-*tert*-leucine **1** with Boc_2O in the presence of K_2CO_3 in an *i*-PrOH–H_2O mixture; the (*S*)-1,2-amino alcohol **3** was prepared by reduction of the amino acid **1** with $LiAlH_4$ in THF; the pseudodipeptide **4** was obtained by the reaction between the resulting compounds **2** and **3** in CH_2Cl_2 with the addition of isobutyl chloroformate and Et_3N (Scheme 1).

2.2. Synthesis and study of the structure of diamidophosphites

The 1,3,2-diazaphospholidine **6** was prepared by condensation of the pseudodipeptide **4** with (5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane **5** in toluene in the presence of an excess of Et_3N as a base (Scheme 2).[34] The phosphorylating reagent **5** was synthesized[35] analogously to known procedures from (*S*)-glutamic acid and anilide.[36,37]

The chemical and enantiomeric purity, as well as the composition, structure and stereochemical features of the diamidophosphite **6** are determined using NMR spectroscopy of 31P, ^{1}H and 13C (including using homo- and heteronuclear correlation APT, DEPT, ^{1}H,1H-COSY, 13C,1H-HSQC, 13C,1H-HMBC). The results of X-ray diffraction analysis of **6** show that this ligand crystallizes into supramolecular assemblies consisting of two molecules connected by hydrogen bonds (Figure 1).

2.3. Pd- and Rh-catalyzed asymmetric reactions

The asymmetric inducer **6** was tested in the Pd-catalysed reaction of asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate **7** with dimethyl malonate, $[Pd(allyl)Cl]_2$ was used as a precatalyst. (up to 84% *ee* of the product **8**) (Scheme 3) The ligandas **6** was also used in the Rh-catalyzed asymmetric hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate **9** in the presence of $[Rh(cod)_2]BF_4$ as a precatalyst (up to 53% *ee* of the product **10**) (Scheme 4).[34]

3. Conclusions

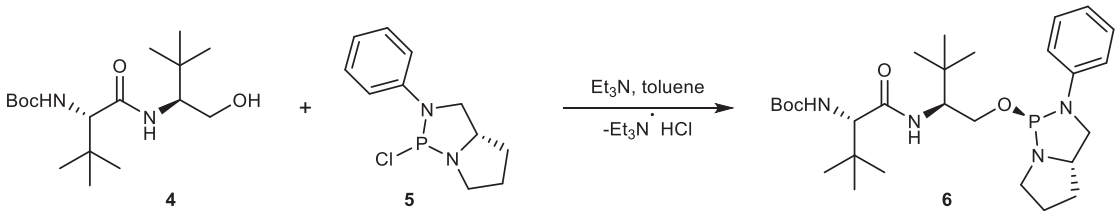
In conclusion, diazaphospholidine **6** with pseudodipeptide substituent was prepared from (*S*)-*tert*-leucine. This ligand was tested in the asymmetric reactions of Pd-catalyzed allylic substitution and Rh-catalyzed ahydrogenation. In general, the ligand has a moderate asymmetric ability.

Our next task is to expand the library of the 1,3,2-diazaphospholidines based on pseudodipeptides and study the coordination behavior of these ligands, as well as their catalytic testing. An attempt to obtain supramolecular catalytic materials based on metal complexes of the 1,3,2-diazaphospholidines with pseudodipeptide substituents is also of interest.

4. Experimental

Synthesis of (2*R*,5*S*)-2-[(*S*)-2-{(*S*)-2-[(*tert*-butoxycarbonyl) amino]-3,3-dimethyl-butanamido}-3,3-dimethylbutyl]-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane 6. To a vigorously stirred solution of phosphorylating agent **5** (0.48 g, 2 mmol) and Et_3N (0.56 mL, 4 mmol) in toluene (15 mL), compound **4** (0.66 g, 2 mmol) was added in one portion at 20 °C. The reaction mixture was stirred at 20 °C for 24 h and passed through a short column filled with SiO_2/Al_2O_3. The filtrate was concentrated *in vacuo* (40 Torr). The residue was dried *in vacuo* (1 Torr) and crystallized from heptane to afford compound **6**.[34]

Asymmetric alkylation of (*E*)-1,3-diphenylallyl acetate 7 with dimethyl malonate. A solution of either $[Pd(allyl)Cl]_2$ (0.0037 g, 0.01 mmol and ligand **6** (0.0107 g, 0.02 mmol or 0.0214 g, 0.04 mmol) in CH_2Cl_2 or THF (5 mL) was stirred for 40 min. Then (*E*)-1,3-diphenylallyl acetate (0.1 mL, 0.5 mmol) was added, the mixture was stirred for 15 min, and treated with dimethyl malonate (0.1 mL, 0.87 mmol), BSA (0.22 mL, 0.87 mmol), and KOAc (0.002 g). The reaction mixture was stirred for 48 h, diluted with hexane (5 mL), and filtered through a short SiO_2 layer. The solvents were removed *in vacuo* (40 Torr) and the residue was dried



Scheme 2. Synthesis of the diamidophosphite 6.

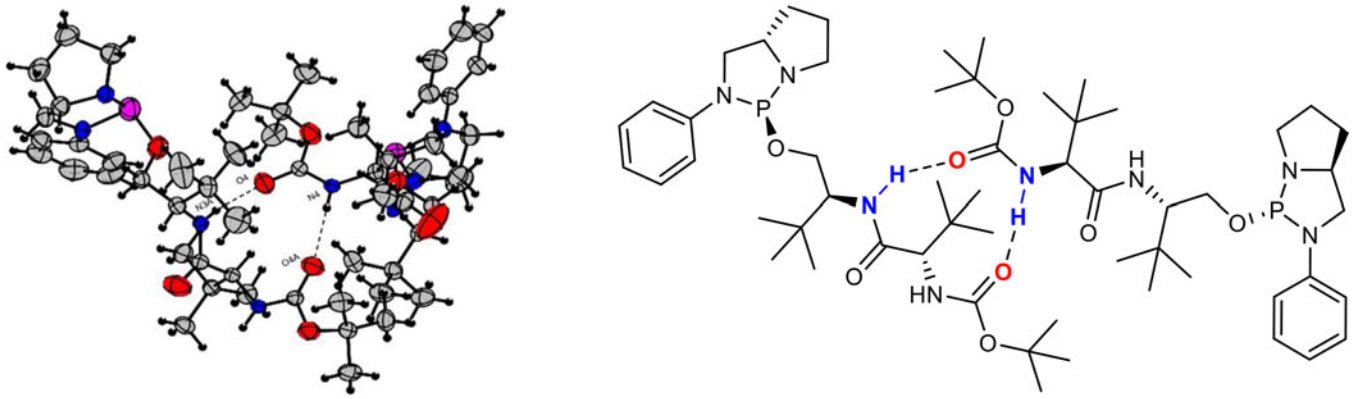
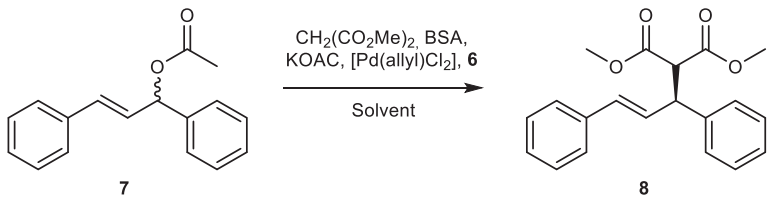
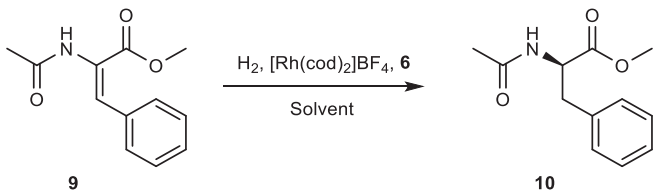


Figure 1. Supramolecular assembly consisting of two molecules **6** according to X-ray diffraction data.



Scheme 3. Pd-catalysed reaction of asymmetric allylic alkylation of (E)-1,3-diphenylallyl acetate 7 with dimethyl malonate.



Scheme 4. Rh-catalyzed asymmetric hydrogenation of (Z)-methyl 2-acetamido-3-phenylacrylate 9.

in vacuo (10 Torr). Conversion of the substrate **7** and enantiomeric excesses of the product **8** were determined by HPLC on a Daicel Chiralcel OD-H chiral column.[34]

Asymmetric hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate 9. A solution of $[Rh(cod)_2]BF_4$ (0.001 g, 0.0025 mmol) and ligand **6** (0.0027 g, 0.005 mmol) CH_2Cl_2 or toluene (2 mL) was stirred for 40 min. Then (*Z*)-methyl 2-acetamido-3-phenylacrylate (0.027 g, 0.125 mmol) was added. Catalytic vessel containing the resulting solution was filled with hydrogen to a pressure of 1.5 atm and the reaction mixture was stirred for 24 h. The volatiles were removed *in vacuo* (40 Torr), the residue was dissolved in diethyl ether (2 mL), filtered through a short SiO_2 layer, concentrated *in vacuo* (40 Torr), and the residue was dried *in vacuo* (10 Torr). Conversion of the substrate **9** and enantiomeric excesses of the products **10** were determined by HPLC on a Daicel Chiralcel OD-H chiral column.[34]

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