First quinine-based aryl phosphite: synthesis and application in the Pd-catalyzed enantioselective rearrangement of allylic thiocarbamate

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New quinine-based polyfunctional aryl phosphite was synthesized. The phosphorus center in the new compound is characterized by a large cone angle (θ = 190°). The new compound can be used in the Pd-catalyzed enantioselective rearrangement of cyclic *O*-allylic thiocarbamate into *S*-allylic thiocarbamate in an optical yield of up to 47% with a quantitative conversion.

Key words: phosphorus-containing quinine derivatives, chiral aryl phosphites, palladium, enantioselective rearrangement, allylic thiocarbamates, cone angle.

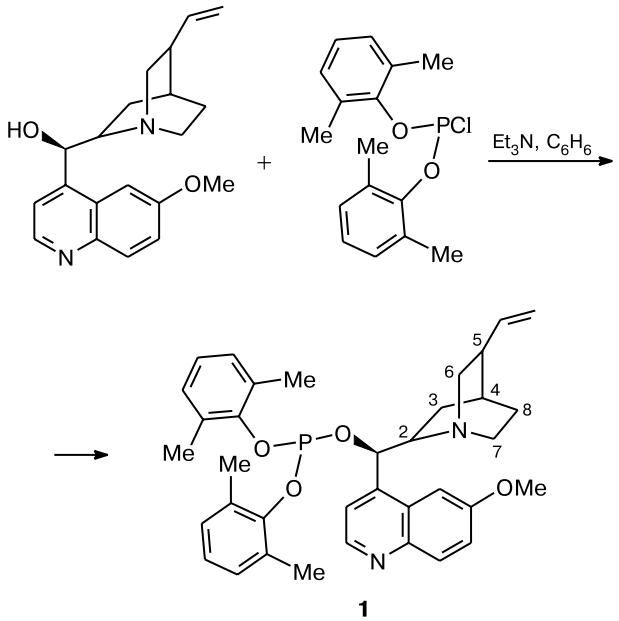
Alkaloids (as well as their various derivatives) are actively used as ligands for asymmetric catalysis due to their structural variability and availability.[1,2] For example, phosphorus-containing derivatives are successfully used in the enantioselective catalytic conjugate addition of organocuprates to enones as well as in hydrogenation and hydrosilylation.[3]

However, only a few phosphites and phosphoramidites containing alkaloid fragments (quinine, codeine, or ephedrine) were used as ligands in the coordination synthesis and catalysis (see Refs. 3—5 and references cited therein). Aryl phosphite derivatives of alkaloids have been previously unknown. In the present study, we report the synthesis of the first representative of this group of phosphorus-containing ligands (**1**) and consider its application in catalysis.

Results and Discussion

Compound **1**, which was prepared by one-step phosphorylation of quinine with the corresponding phosphorochloridite (Scheme 1), is readily soluble in most of organic solvents and stable under an anhydrous atmosphere for several months. Compound **1** belongs to polyfunctional ligands because it contains the donor P atom and two donor N atoms of different nature. The fact that this ligand bears several asymmetric atoms, including N atoms, is also of importance. In addition, the phosphorus center in aryl phosphite **1** is characterized by a large

Scheme 1



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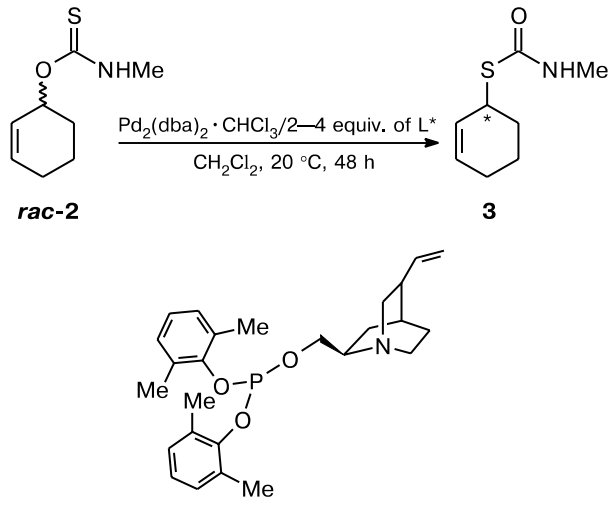
cone angle[6] ($\theta = 190°$; the angle was determined by the semiempirical AM1 quantum-chemical method[7]). This angle is larger than the corresponding angles even in such sterically hindered compounds as phosphite derivatives of calixarenes ($\theta = 160$—$176°$).[8] Hence, compound **1** is a promising ligand for asymmetric catalysis.

In particular, ligand **1** was used in the enantioselective rearrangement of *O*-allylic thiocarbamate **2** into *S*-allylic thiocarbamate **3** (Scheme 2). It should be noted that the conversion of the substrate and the optical yield were increased as the **1**/Pd molar ratio was increased. Thus, the conversion was 57% with *ee* 37% (*S*) and 100% with *ee* 47% (*S*) at **1**/Pd = 1 and 2, respectively.

Scheme 2



dba is dibenzylideneacetone, L* = **1** or **4**

The presence of the quinoline core in ligand **1** is a necessary condition for the attainment of a noticeable stereoinduction. Thus, quincoridine-based aryl phosphite **4** prepared by us earlier appeared to be completely nonselective. In this reaction, we achieved only 2% *ee* (*S*) with the conversion of 60% (see Scheme 2).

Apparently, the low selectivity is attributable to the fact that the quinoline fragment of phosphite **1** contains the sp^2-hybridized donor N atom capable of being involved in additional coordination to the metal atom.[3] It should also be taken into account that the phosphorus center in ligand **4** has a substantially smaller cone angle ($\theta = 157°$).

It should be noted that the (*S*) enantiomer of compound **3** has been prepared recently[9] with the nearly quantitative optical purity. Nevertheless, the high degree of enantioselectivity achieved in the reaction with the use of ligand **1** demonstrates that this ligand has a high potential as a stereoinducing reagent. This potential would be expected to be manifested in other asymmetric reactions. In addition, this is presently the only example of the involvement of chiral phosphites in catalytic enantioselective rearrangements.

Experimental

The ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AMX-400 instrument (400.13 MHz for ^1H, with respect to Me_4Si; 100.61 MHz for ^{13}C, with respect to $CDCl_3$, δ_C 76.91; 161.98 MHz for ^{31}P, with respect to a 85% H_3PO_4 solution in D_2O). The assignment of the signals in the ^{13}C NMR spectrum of ligand **1** was made with the use of the DEPT procedure and using the data published earlier.[10] The optical rotation was measured on a Perkin—Elmer 141 instrument. The mass spectra (EI, 70 eV) were obtained on a Varian MAT-311 instrument. The conversion of substrate **2** was monitored by ^1H NMR spectroscopy. The optical yield of compound **3** was determined by GC with the use of an octakis(6-*O*-methyl-2,3-*O*-dipentyl)-γ-cyclodextrin chiral column as described previously.[9]

The starting substrate **2** was synthesized according to a known procedure.[11]

All reactions were carried out under an atmosphere of dry argon with the use of anhydrous solvents.

Di(2,6-dimethylphenyl) [(5-vinylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl] phosphite (1). A solution of di(2,6-dimethylphenyl) chlorophosphite[12] (0.842 g, 2.7 mmol) in benzene (8 mL) was added dropwise to a solution of quinine (0.876 g, 2.7 mmol) and Et_3N (0.4 mL, 2.7 mmol) in benzene (25 mL) with intense stirring and cooling to 0 °C. The resulting solution was heated to boiling, cooled to ~20 °C, and filtered off. The filtrate was concentrated *in vacuo* (40 Torr) and hexane (25 mL) was added to the residue. The precipitate that formed was filtered off. The filtrate was concentrated *in vacuo* (40 Torr) and then kept *in vacuo* (1 Torr) at 50 °C for 2 h. Compound **1** was obtained in a yield of 1.40 g (87%) as a white viscous substance, $[\alpha]_D^{23}$ −212.2 (*c* 0.8, $CHCl_3$). Found (%): C, 72.21; H, 7.16; N, 4.82; P, 5.30. $C_{36}P_{41}N_2O_4P$. Calculated (%): C, 72.46; H, 6.93; N, 4.69; P, 5.19.

^{13}C NMR (C_6D_6), δ: 158.10—101.69 (C_{Ar}); 142.19 (s, CH=); 114.14 (s, CH_2=); 75.41 (d, CHOP, $^2J_{C,P} = 15.2$ Hz); 61.20 (d, C(2), $^3J_{C,P} = 6.8$ Hz); 56.88 (s, C(6)); 54.98 (s, MeO); 42.53 (s, C(7)); 40.18 (s, C(5)); 28.09 (s, C(4)); 27.94 (s, C(8)); 23.21 (s, C(3)); 18.15, 18.08, 17.91, and 17.85 (all s, Me(Ar)). ^{31}P NMR (C_6D_6), δ: 147.73. MS, *m/z* (I_{rel} (%)): 596 $[M]^+$ (2), 475 $[M - Me_2C_6H_3]^+$ (23), 307 $[M - (Me_2C_6H_3O)_2PO]^+$ (75), 122 $[Me_2C_6H_3OH]^+$ (100).

Palladium-catalyzed rearrangement of *O*-allylic thiocarbamate 2 into *S*-allylic thiocarbamate 3. A solution of $Pd_2(dba)_3 \cdot CHCl_3$ (0.009 g, $8.5 \cdot 10^{-6}$ mol, 1.7 mol.%) and ligand **1** (0.012 g, $2 \cdot 10^{-5}$ mol, 2 mol.% or 0.024 g, $4 \cdot 10^{-5}$ mol, 4 mol.%) in CH_2Cl_2 (5 mL) was stirred for 20 min. Then substrate **2** (0.171 g, 0.001 mol) was added. The resulting solution was kept at 20 °C for 48 h, a saturated NaCl solution (10 mL) was added, and the reaction mixture was stirred for 1 h. The product was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* (40 Torr). The residue (yellow oil) was chromatographed on a column (2×30) with silica gel Kieselgel 60 (0.04—0.06 mm, Merck) using a 4 : 1 pentane—EtOAc mixture as the eluent.

The eluent was removed *in vacuo* (40 Torr). *S*-(2-Cyclohexenyl) *N*-methylthiocarbamate (**3**) was obtained as a white crystalline compound in a yield of 0.093 g (54%) or 0.166 g (97%), respectively, m.p. 56.2—57.2 °C (from hexane). The spectroscopic data are in agreement with the published data.[11] ^{1}H NMR ($CDCl_3$), δ: 1.40—2.40 (m, 6 H, CH_2); 2.85 (d, 3 H, NMe, J = 5.6 Hz); 4.20 (br.m, 1 H, SCH); 5.35 (br.s, 1 H, NH); 5.65 and 5.70 (both br.s, 1 H each, CH).

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