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A new efficient synthesis of Pyrphos ligand

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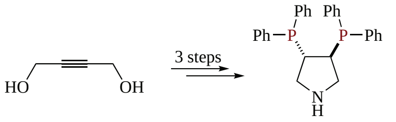
A new efficient synthesis of racemic (*R,*R**)-Pyrphos ligand based on aza-Michael addition reaction of 2,3-bis(diphenylphosphoryl)buta-1,3-diene with ammonia followed by the reduction of resulting 3,4-bis(diphenylphosphoryl)pyrrolidine is proposed. The starting reactants are available but-2-yne-1,4-diol and chloro(diphenyl)phosphine.**



rac-(*R**,*R**)-Pyrphos

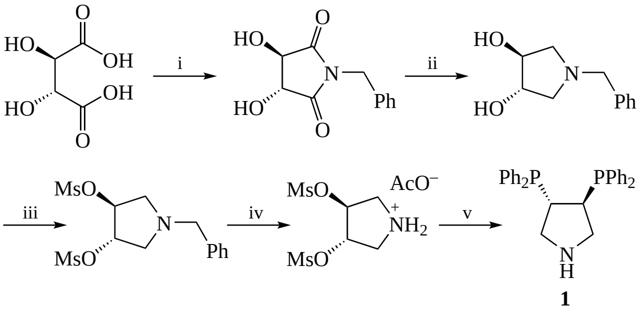
- only 3 synthetic steps
- mild reaction conditions
- cheap and commercially available reagents

Keywords: Pyrphos, aza-Michael addition, intramolecular cyclization, reduction, phosphines, X-ray analysis.

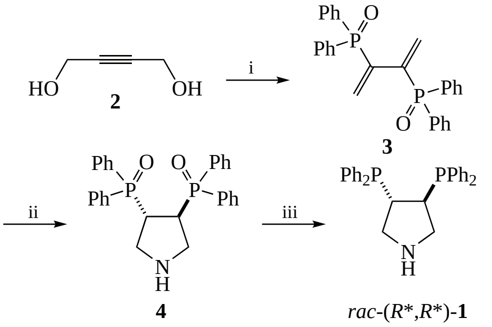
The synthesis of new catalysts as well as an optimization of methods for the preparation of well-known ones, to reduce their cost, have attracted great attention over the past decades. Phosphorous-containing ligands such as phosphines[1–4] and phosphine oxides[5–8] are the most common ones. Among wide variety of phosphine ligands, (3*R*,4*R*)-3,4-bis(diphenylphosphino)pyrrolidine, (*R*,*R*)-Pyrphos, **1** (Scheme 1) and its derivatives are very popular for preparing catalysts based on transition metals such as Rh,[9] Pd,[9–11] or Pt.[12,13] Rhodium(I) complexes with (*R*,*R*)-Pyrphos derivatives are widely used as catalysts for asymmetric hydrogenation of α-(acylamino)acrylic acids to (*S*)-*N*-acylamino acids,[14–19] and itaconic acid derivatives.[20–22] Platinum(II) complexes with Pyrphos are utilized for catalytic epoxidation of olefins,[12] and for the enantioselective Baeyer–Villiger oxidation of cyclic ketones with hydrogen peroxide.[13] Pyrphos is also used for the grafting on various supports to obtain corresponding catalysts with improved catalytic activity. Pyrphos-functionalized ionic liquids with [Rh(COD)$_2$]BF$_4$ exhibited high catalytic activity and enantioselectivity in asymmetric hydrogenation of α-acetamidocinnamic acid in [bmim]BF$_4$/MeOH cosolvent systems.[23] Pyrphos ligand attachment to dendrimers has found widespread application. For this purpose, poly(propyleneimine),[24] poly(amidoamine),[25,26] Frechet-type polyether,[27,28] and poly(aryl ether)[29] dendrimers were used. Also, Pyrphos was grafted on polyethylene glycol,[30] poly(ethylene oxide)–styrene matrix,[11] silica,[31] gold nanoparticles,[32] and carbon nanotubes.[33] Metal conjugated protein markers based on Pyrphos (*R*,*R*) ligand were studied.[34]

Firstly, (*R*,*R*)-Pyrphos **1** was synthesized by Nagel in 1984 in seven steps from natural (*R*,*R*)-(+)-tartaric acid **2**.[14] Then, in 1986 the same team has optimized the procedure up to five steps, which is still in use today (see Scheme 1).[16] However, this complex method significantly increases the cost of the ligand and limits its widespread use. Therefore, a development of a new low-cost method of synthesis of Pyrphos ligand is a topical issue today.

Herein, we report a facile method for the preparation of racemic (*R**,*R**)-Pyrphos ligand *rac*-**1** starting from available but-2-yne-1,4-diol **2** (Scheme 2). In contrast to the Nagel's five-step synthesis, the proposed method contains only three synthetic steps, which significantly reduces the production cost. At the first step, *via* a double [2,3]-sigmatropic rearrangement[35] but-2-yne-1,4-diol **2** was converted into 2,3-bis(diphenylphosphoryl)buta-1,3-diene **3** upon treatment with chloro(diphenyl)phosphine in THF. The second step was the aza-Michael addition of ammonia to electron-deficient diene **3** followed by intramolecular cyclization with a formation of 3,4-bis(diphenylphosphoryl)pyrrolidine **4**. This reaction was carried out in an autoclave at 60 °C in the presence of 20-fold excess of ammonia and small



Scheme 1 *Reagents and conditions*: i, BnNH$_2$; ii, NaBH$_4$/BF$_3$; iii, Ms$_2$O; H$_2$, Pd/C, AcOH; iv, Ph$_2$PNa (see ref. 16).



Scheme 2 *Reagents and conditions*: i, Ph$_2$PCl, Py, THF; ii, NH$_3$, MeOH, 60 °C, autoclave; iii, PhSiH$_3$, 120 °C (neat).

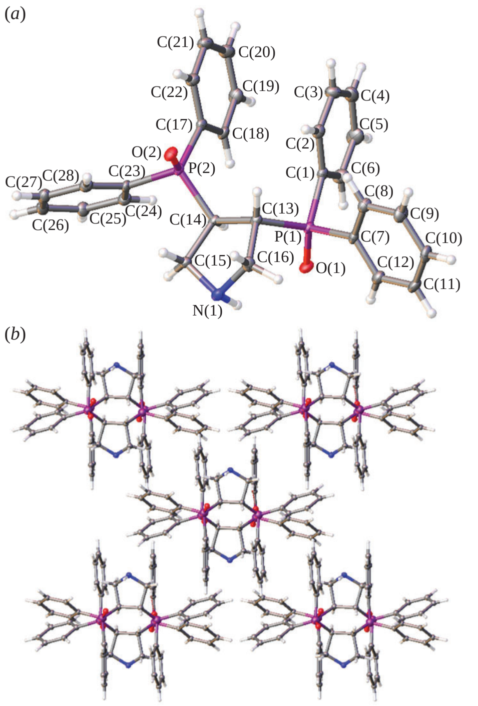
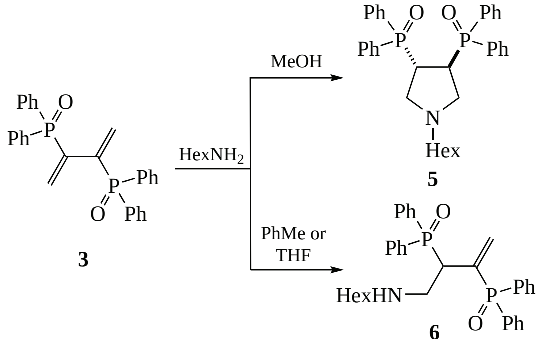


Figure 1 (*a*) Molecular structure and (*b*) crystal packing of compound **4** presented as ADP ellipsoids at 50% probability. C (grey), O (red), N (blue), P (violet), H (white).

amount of methanol, which provided almost quantitative yield (up to 91%). Compound **4** could be easily purified by column chromatography on silica using a dichloromethane–methanol (3 : 1) mixture as an eluent.

The crystal structure of compound **4** was determined by X-ray diffraction analysis (Figure 1).† Crystals of **4** have triclinic syngony. An independent part consists of one molecule. The nitrogen atom retains the sp^3-hybridization in the crystal. The agile amino-hydrogen forms a weak banana-interaction with *p*-orbital of nearest oxygen [O(1), same molecule]. Phenyl groups [C(1)–C(6)] and [C(17)–C(22)] participate in intramolecular and intermolecular stacking interactions {[C(1)–C(6)] to [C(17)–C(22)]: centroid to plane distance = = 3.578(4) Å, twist angle = 8.0(3)°, plane shift = 2.008(6) Å; [C(1)–C(6)] to [C(1)–C(6)]: centroid to plane distance = = 3.584(4) Å, twist angle = 0.0°, plane shift = 1.465(7) Å; [C(17)–C(22)] to [C(17)–C(22)]: centroid to plane distance = = 3.656(4) Å, twist angle = 0.0°, plane shift = 1.579(7) Å}. The π-system of phenyl groups [C(7)–C(12)] and [C(23)–C(28)] is involved only in intermolecular C–H···π interactions. The packing motif is similar to the distorted hexagonal stacking (see Figures 1 and S15 from Online Supplementary Materials).



Scheme 3

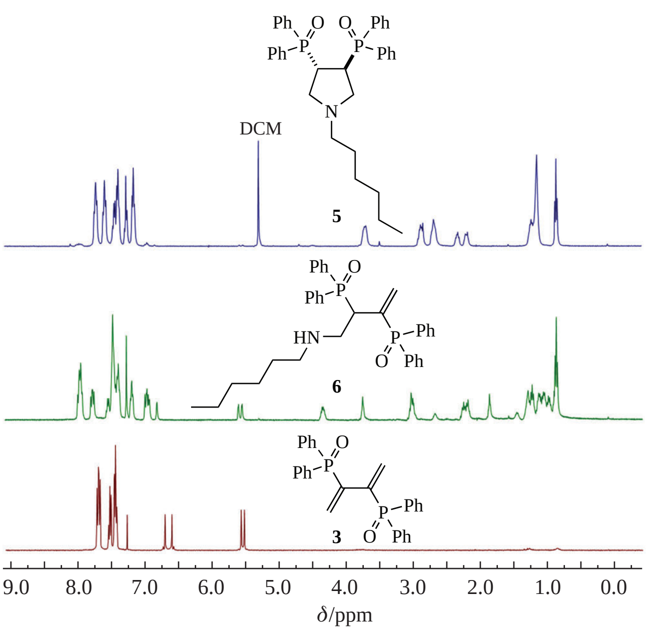


Figure 2 ^{1}H NMR spectra of compounds **3**, **5** and **6**.

Further, routine reduction of phosphine oxide groups[39] in **4** with neat phenylsilane at 120 °C, similarly to the described method,[40] gave the target Pyrphos *rac*-**1** in a good yield (up to 73% by NMR). ^{31}P NMR spectrum of **1** ($CDCl_3$, see Online Supplementary Materials, Figure S6) shows the full conversion of initial compound **4** after 24 h, namely, phosphorous signal shifts from 35.33 ppm in compound **4** to –7.05 ppm in compound **1**.

With the use of *n*-hexylamine as an example of alkylamine and polar protic solvents such as MeOH, EtOH in the studied aza-Michael addition reaction, *N*-hexyl-substituted 3,4-bis(diphenylphosphoryl)pyrrolidine **5** was obtained (Scheme 3, *cf.* ref. 41). However, when aprotic toluene or THF are used, the addition occurs without intramolecular cyclization to afford adduct **6**. This is clearly seen from ^{1}H NMR spectra (Figure 2).

To conclude, a new efficient synthesis of racemic (*R**,*R**)-Pyrphos ligand based on aza-Michael addition reaction of 2,3-bis(diphenylphosphoryl)buta-1,3-diene with ammonia followed by the reduction of the resulting *rac*-(3*R**,4*R**)-3,4-bis(diphenylphosphoryl)pyrrolidine is developed. The method seems promising since the separation of the enantiomers of *rac*-**1** or its precursor *rac*-**4** is a challenge.

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† *Crystal data for* **4**. $C_{28}H_{27}NO_2P_2$ (M = 471.44), triclinic, space group $P\bar{1}$ at 100 K: a = 10.750(3), b = 11.328(3) and c = 11.464(3) Å, α = 68.292(9), β = 81.297(9) and γ = 69.240(9)°, Z = 2, d_{calc} = 1.291 g cm^{-3}, V = 1212.5(5) Å^3, μ(MoKα) = 0.205 mm^{-1}. A total of 7386 reflections were collected (7386 independent reflections, R_{int} = 0.1389), GOOF 1.066, final R_1 indices [$I > 2\sigma(I)$] = 0.0862 and final wR_2 indices [all data] = 0.2173. Largest diff. peak/hole = = 1.04/–0.68 e Å^{-3}. Crystallographic data were collected on a Bruker D8 QUEST diffractometer with a CCD area detector with λ(MoKα) = 0.71073 Å at 100 K. Using Olex2,[36] the structure was solved with the XT[37] structure solution program using Intrinsic Phasing and refined with the XL[38] refinement package using Least Squares minimization.

CCDC 2255112 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

study was performed using research equipment of the Molecular Structure Investigation Center of the Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.015.

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