Pd-catalyzed asymmetric allylation of an *o*-carborane derivative

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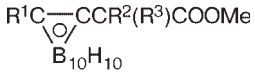
The asymmetric synthesis of methyl 2-phenyl-2-(2-phenyl-*ortho*-carboran-1-yl)pent-4-enoate was carried out by palladium-catalyzed allylation in the presence of amino phosphites of the type $(RO)_2P—O—CH_2—CHR´—NR''_2$ as chiral ligands.

Key words: asymmetric allylation, palladium, *P*,*N*-ligands, amino phosphites, carboranes.

A high content of the boron atoms in carborane derivatives has made them attractive for use in boron neutron-capture therapy of cancer.[1,2] Recently, it was found that the spherical geometry and hydrophobic character of the carborane framework can be used for the synthesis of physiologically active carborane-based compounds.[3,4] In the case of chiral compounds, medicinal drugs should usually be prepared only from individual enantiomers.[5] Carborane derivatives containing an asymmetric carbon atom in the side chain are obtained by introducing carborane-containing fragments into chiral compounds.[6] In the present work, the direct asymmetric synthesis of an *o*-carborane derivative was carried out for the first time by Pd-catalyzed allylation in the presence of chiral ligands.

Earlier,[7] it was shown that methyl *ortho*-carboranylacetates **1a,b** are rather strong CH acids like dialkyl malonates or β-oxo esters. With a palladium complex as a catalyst, compounds **1a,b** react with allyl carbonates to give the corresponding racemic allyl derivatives **1c,d**.



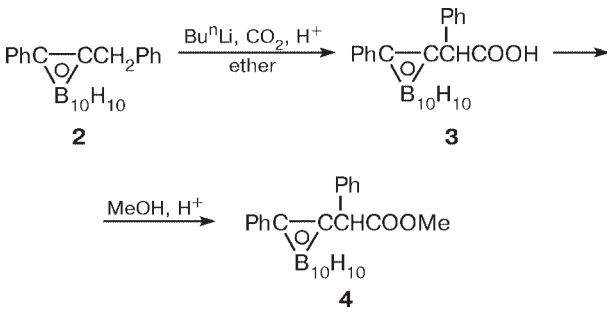
1a—d

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
1a	Ph	H	H	**1c**	Ph	All	H
1b	Me	H	H	**1d**	Me	All	H

Products **1c,d** containing an asymmetric tertiary carbon atom can undergo racemization through the formation of an enol form, which prevents their resolution into individual enantiomers.

For this reason, methyl 1-(2-phenyl-*ortho*-carboran-1-yl)phenylacetate **4** containing the tertiary carbon atom was prepared from 2-benzyl-1-phenyl-*ortho*-carborane **2** and used as a starting carborane-containing CH acid for the asymmetric synthesis (Scheme 1).

Scheme 1



Its allylation product will contain a quaternary asymmetric carbon atom, which makes racemization impossible. Racemic ester **4** reacts with methyl prop-2-enyl carbonate **5** in the presence of palladium complexes containing chiral ligands to give optically active allylation product **6** (Scheme 2).

This reaction falls into a special type of asymmetric allylation. As a rule, a new asymmetric center appears at either terminal carbon atom of the allyl fragment. Such systems are widely described in the literature, and many of them have been obtained in high optical yields.[8,9] In our case, the new asymmetric center appears at the carbon atom of the nucleophile. The stereoselectivity of such

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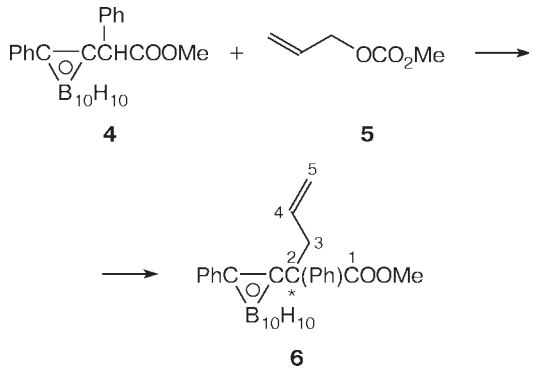
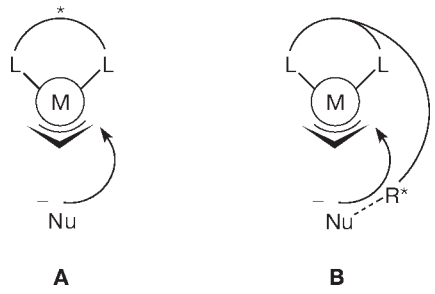
Scheme 2



Reagents and conditions: 2 mol. % $[(\pi\text{-}C_3H_5)PdCl]_2$, 4 mol. % ligand L*, THF, 20 °C, 20 days, BSA, KOAc.

allylation is difficult to control since the nucleophile approaches the allyl fragment of an intermediate η^3-allylpalladium(II) complex from the side opposite the transition metal atom and, accordingly, the coordinated chiral ligand.

Scheme 3

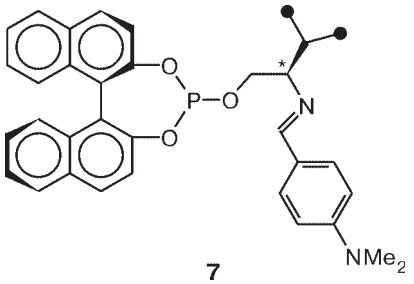


For the first time, the asymmetric allylation of this type has been reported[10] for cyclic β-diketones with (+)-DIOP as a chiral ligand, but the optical yield did not exceed 10%. Based on the allylation mechanism,[8] the authors[10] attributed such a low enantioselectivity to a very long distance between the chiral fragment of the ligand and the new asymmetric center (Scheme 3, **A**). To solve this problem, new diphosphine ligands containing chiral functional groups at a certain distance from the phosphorus atoms were synthesized.[11] It was expected that these functional groups would be able to reach the opposite side of the η^3-allyl ligand in the intermediate complex and effectively interact with the approaching nucleophile to increase the enantioselectivity of the reaction (Scheme 3, **B**). In this case, the optical yield was 52% at −55 °C and no higher than 19% at room temperature. At the same time, it was (+)-DIOP that provided the highest optical yield (57%) among phosphine ligands in the allylation of a glycine derivative.[12] The allylation of five-membered cyclic β-oxo ester in the presence of QUIPHOS[13] as a chiral ligand gives the corresponding product in 95% *ee*. Interestingly, the enantioselectivity for a six-membered ring proves to be much lower (10%). Isocyanocarboxylates,[14] α-nitro ketones, α-nitro esters,[15] and 1,5-dimethylbarbituric acid[16] were also used, along with β-dicarbonyl compounds and amino acid derivatives, as nucleophiles in reactions of this type. Although this problem is under extensive study, it is still difficult to say what regularities one should be guided by in order to obtain allylation products in high *ee*.

The studied allylation of ester **4** with compound **5** proceeds very slowly and gives low yields. Apparently, this is due to a high Gibbs energy for the formation of a tertiary carbanion from the starting carborane-containing ester **4** and to steric hindrances presented by the bulky carboranyl group in the tertiary carbanion during its attack on the intermediate π-allylpalladium complex. The reactions of this type are characterized by a low reaction rate.

A catalytically active complex was prepared *in situ* by replacing the ligand in a precatalyst by an optically active ligand. π-Allylpalladium chloride was used as the precatalyst. The reaction proceeds in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as a base and catalytic amounts of KOAc.

The chiral ligands were *P*,*N*-bidentate derivatives of phosphorous acid (amino phosphites) **7**—**13** containing three bridging atoms between the P and N atoms and, for comparison, such classic phosphine *P*,*P*-bidentate ligands as (+)-DIOP **14** and (+)-BINAP **15**.



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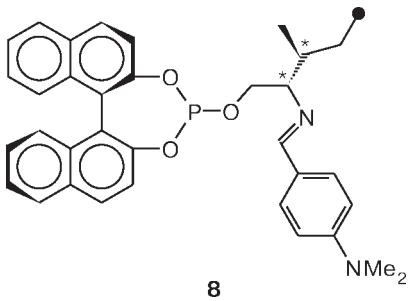

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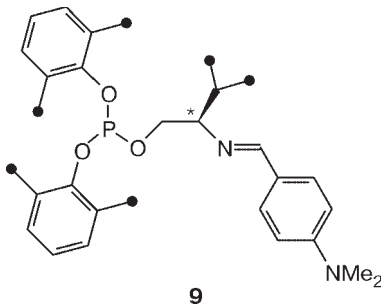

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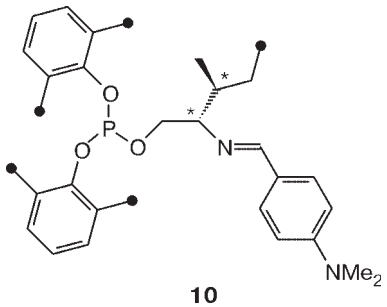

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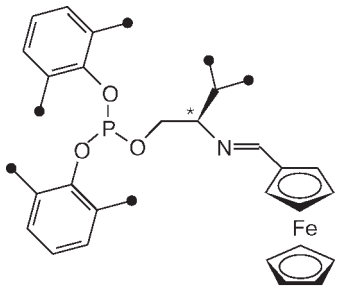

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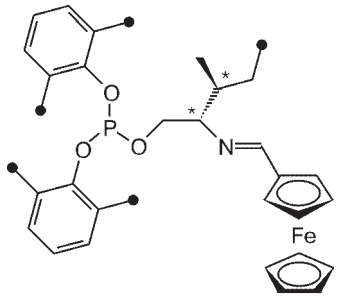

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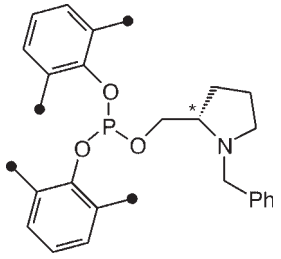

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At present, the number of papers devoted to the use of phosphite ligands in catalytic processes becomes increasingly high.[17] In these compounds, the phosphorus coordination sphere includes oxygen heteroatoms, which reduces the π-donating ability of the phosphorus center and, accordingly, enhances the electrophilicity of the transition metal atom. It should also be noted that phosphorous acid esters are easily available from the corresponding amino alcohols.[18,19] Very recently, we demonstrated that some amino and amido phosphites can be used as ligands in the Pd-catalyzed allylation of CH acids.[20]

Table 1. Pd-catalyzed allylation of ester **4** with methyl prop-2-enyl carbonate **5** in THF at 20 °C

Ligand	Yield (%)	*ee* (%)	Ligand	Yield (%)	*ee* (%)
7	98	6	**12**	29	32
8	5	9	**13**	5	4
9	45	25	**14**	25	20
10	25	19	**15**	49	4
11	29	24			

The results obtained in the allylation of ester **4** in THF are given in Table 1. It can be seen that the use of amino phosphites as chiral ligands affords an optically active allylation product. Although the optical purity of the product is low (≤32%), its value occasionally exceeds the *ee* reached under the same conditions with such classic chiral diphosphine ligands as (+)-DIOP **14** and (+)-BINAP **15**. This indicates that amino phosphites are a promising source of more efficient ligands for the Pd-catalyzed asymmetric allylation of CH acids. Indeed, such ligands were synthesized and used by us in the allylation of carborane **4** to increase an optical yield of the product.[19]

Experimental

^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer (400.13 MHz) in $CDCl_3$. Mass spectra (EI, 70 eV) were recorded on a Kratos MS 890 instrument. Optical yields were determined using HPLC with a Varian 5000 chromatograph (a WHELK-01 chiral column (R,R), hexane : Pr^iOH = 99 : 1, 1 mL min^{-1}, 254-nm UV detector). Catalyzed reactions and metalation were carried out in an atmosphere of dry argon. Solvents were distilled before use (THF and ether over sodium benzophenone ketyl and MeOH over CaH_2). Compounds **2** [21] and **5** [22] were prepared according to the known procedures. The course of the reactions were monitored by TLC on Silufol UV 254 plates.

1-(2-Phenyl-*ortho*-carboran-1-yl)phenylacetic acid (3). A 1.6 *M* solution of Bu^nLi (22 mL) was added to a stirred solution of carborane **2** (9.5 g, 0.03 mol) in 200 mL of anhydrous ether. The reaction mixture was stirred for 0.5 h; then dry CO_2 was passed through it for 40 min, and a saturated aqueous solution of NH_4Cl (250 mL) was added. The organic layer was separated, and the product from the aqueous layer was extracted with ether (2×100 mL). The ethereal layers were combined, washed with a solution of $NaHCO_3$ (2×100 mL) and water (100 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was recrystallized from *n*-heptane to give acid **3** (9.60 g, 90%) as small white crystals, m.p. 224—225 °C. ^{1}H NMR ($CDCl_3$), δ: 3.77 (s, 1 H, CH); 7.01—7.63 (m, 10 H, 2 Ph). MS, *m/z*: 354 $[M]^+$.

Methyl 1-(2-phenyl-*ortho*-carboran-1-yl)phenylacetate (4). Acid **3** (9.50 g, 0.027 mol) was dissolved in 250 mL of anhydrous MeOH. Then conc. H_2SO_4 (2 mL) was added, and the reaction mixture was refluxed for 96 h without access for atmospheric moisture. The greater part of the solvent was removed. The crystalline white precipitate that formed was filtered off and recrystallized from MeOH. Yield 8.50 g (85%), m.p. 131—132 °C. ^{1}H NMR ($CDCl_3$), δ: 3.60 (s, 3 H, OMe); 3.78 (s, 1 H, CH); 6.98 (br.d, 2 *o*-H, ^3J = 6.8 Hz) + 7.20 (br.t, 2 *m*-H, ^3J = 7.2 Hz) + 7.28 (tt, 1 *p*-H, ^3J = 7.2 Hz, ^4J = 1.2 Hz) (5 H, Ph—$C_2B_{10}H_{10}$); 7.42 (br.t, 2 *m*-H, ^3J = 7.6 Hz) + 7.53 (tt, 1 *p*-H, ^3J = 7.2 Hz, ^4J = 1.2 Hz) + 7.59 (br.d, 2 *o*-H, ^3J = 7.6 Hz) (5 H, Ph—CH). MS, *m/z*: 368 $[M]^+$. Found (%): C, 55.72; H, 6.48; B, 29.34. $C_{17}H_{24}B_{10}O_2$. Calculated (%): C, 55.41; H, 6.57; B, 29.34.

Palladium-catalyzed allylation of ester 4 with methyl prop-2-enyl carbonate 5 (general procedure). A solution of $[(\pi\text{-}C_3H_5)PdCl]_2$ (3.7 mg, 0.01 mmol) and the ligand (0.02 mmol) in 4 mL of THF or CH_2Cl_2 was stirred for 20 min. Then ester **4** (185 mg, 0.5 mmol), carbonate **5** (0.12 mL, 1 mmol), BSA (0.15 mL, 0.6 mmol), and anhydrous KOAc (3 mg, 0.03 mmol) were added. The resulting homogeneous solution was kept at ~20 °C for 20 days. The greater part of the solvent was removed, and the residue was dissolved in 30 mL of ether and washed with 5% HCl (2×20 mL), a saturated solution of $NaHCO_3$ (20 mL), and water. The ethereal layer was dried over Na_2SO_4. The ether was removed at a reduced pressure, and the residue (yellow oil) was chromatographed on a SiO_2-covered plate (17×23 cm) in light petroleum—EtOAc (7 : 1). The eluent was removed at a reduced pressure to give allylation product **6** as a yellow oil. ^{1}H NMR ($CDCl_3$), δ: 3.15 + 3.22 (1 H + 1 H, AB system, $H_AC(3) + H_BC(3)$, $^2J_{AB}$ = 14.4 Hz, $^3J_{A,H(1)}$ = 7.2 Hz, $^3J_{B,H(1)}$ = 5.6 Hz, $^4J_{A,H(2)} = {}^4J_{A,H(3)}$ = 1.2 Hz, $^4J_{B,H(2)} = {}^4J_{B,H(3)}$ = 1.4 Hz); 3.53 (s, 3 H, CH_3); 4.87 (dm, 1 H, H(2), $^3J_{H(2),H(3)}$ = 10.2 Hz); 4.95 (dm, 1 H, H(3), $^3J_{H(1),H(3)}$ = 17.0 Hz); 5.18 (m, 1 H, H(1)); 7.05—7.40 (m, 10 H, 2 Ph). MS, *m/z*: 408 $[M]^+$.

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