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Synthesis of 4,4-dimethyl-3,5-bis-(diphenylphosphino)cyclohexanone

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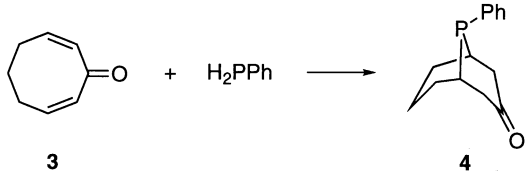
Abstract—The title diphosphine **1** has been synthesized by double Michael addition of diphenylphosphine to 4,4-dimethyl-2,5-cyclohexadienone (**2**). NMR spectroscopy revealed that instead of the desired *cis* adduct **1a**, which is of interest as a bidentate ligand for transition metal centers, the *trans* isomer **1b** had been obtained. This was rationalized by analyzing the stereochemistry of intermediates in this reaction. Attempted conversion of **1b** to the thermodynamically more stable **1a** by oxidation to the bisphosphine oxide **5** followed by base catalyzed equilibration was thwarted by decomposition in the second step. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Diphosphines play an important role as bidentate ligands in homogeneous catalysis.[1] Some of the more recent diphosphines are not the more classical 1,2-diphosphines where the resulting metal complex involves a five-membered ring, but 1,3-diphosphines giving rise to six-membered ring metal complexes with new and interesting activities. 1,3-Diphosphines can be prepared using established methods, but our goal is to synthesize these ligands with extra functionality and via simple and environmentally friendly ways.



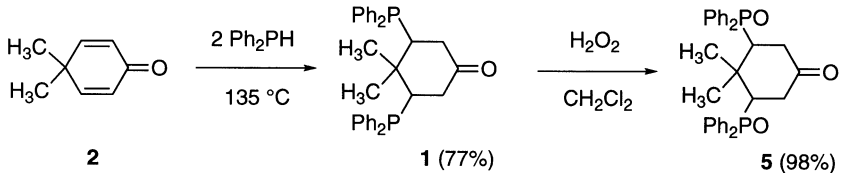
Scheme 1.

We envisaged that for this purpose, 4,4-dimethyl-3,5-bis(diphenylphosphino)cyclohexanone (**1**) and its derivatives might be attractive ligands. Moreover, the synthesis of **1** by reacting two equivalents of diphenylphosphine with 4,4-dimethyl-2,5-cyclohexadienone (**2**)[2] promised to be short and attractive in view of the well-documented addition of secondary and primary phosphines to double bonds.[3] In particular, the double addition of phenylphosphine to 2,7-cyclooctadienone (**3**) under formation of **4**[4] (Scheme 1) was considered to be an encouraging precedent.

2. Results and discussion

It turned out that in principle, this concept could be realized. On heating a mixture of **2** with two equivalents of diphenylphosphine under nitrogen for 10 h to 130–135°C, double Michael addition occurred and **1** was isolated in 77% yield (Scheme 2).

However, a detailed analysis of the NMR spectra showed that while **1** did have the expected structure, its stereo-



Scheme 2.

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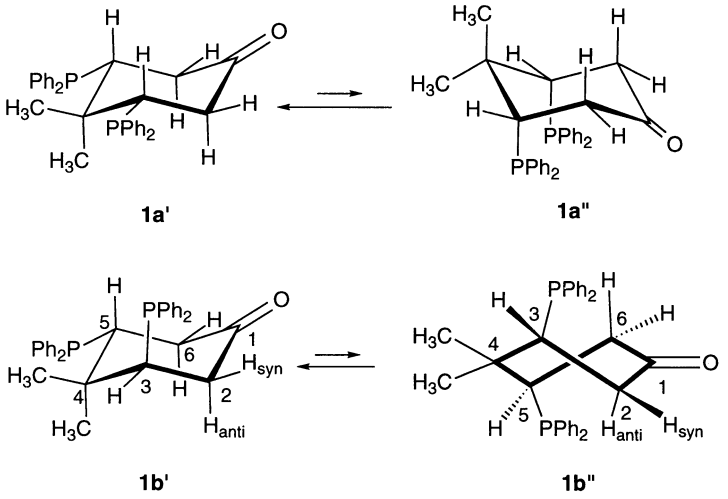
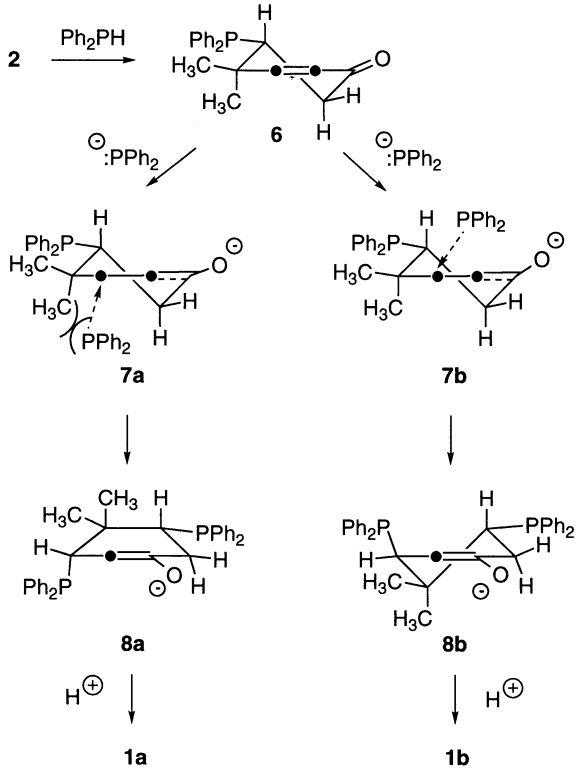


Scheme 3.

chemistry was not suitable for bidentate coordination; for this purpose, both diphenylphosphino substituents should reside on the same side of the six-membered ring. In this case, the most stable conformation would be **1a**′ (Scheme 3) with a diequatorial arrangement of these substituents, but a chair–chair inversion would lead to **1a**″ which is suitable for bidentate coordination to a metal center, even though the ligands are in the less stable diaxial orientation.

In both **1a**′ and (the less likely) **1a**″, the two methyl groups are *nonequivalent* and should appear as two signals with different proton and carbon chemical shifts; the carbon signals should be triplets because they are coupled to two identical phosphorus nuclei. However, we observed the methyl groups to be magnetically *equivalent* ($\delta(^1H)=1.24$, s; $\delta(^{13}C)=27.7$, dd) with *different* couplings to phosphorus ($^3J(CP)=12.9$ Hz, $^3J(CP)=9.1$ Hz); again, the two phosphorus nuclei are magnetically equivalent ($\delta(^{31}P)=-11.3$). This excludes a *cis* arrangement of the diphenyl phosphino groups and thus any conformation of **1a**.



Scheme 4. ·=CH.

On the other hand, the spectra do support a *trans* arrangement as in **1b**. The two most favorable conformations appear to be a (rapidly equilibrating) chair conformer **1b**′ and the twist boat **1b**″, both of which are in line with simulation. Both conformations have unfavorable aspects. Normally, the twist boat has an energetic disadvantage of 4–5 kcal mol^{-1} relative to the chair. On the other hand, the axial orientation of the diphenylphosphino group in **1b**′ with an estimated conformational energy in the range of $\Delta G=$ 2–3 kcal mol^{-1} will make an unfavorable contribution. This results in a difference of at least 1–3 kcal mol^{-1} in favor of **1b**′ which will be further increased due to the presence of the sp^2 carbon of the carbonyl group as it reduces the (normally double) 1,3-diaxial repulsion of the axial substituent.[5] We therefore believe that **1b** actually adopts the chair conformation of **1b**′.

As **1a**′ with its diequatorial arrangement of the two diphenylphosphino groups is undoubtedly the most stable stereoisomer of **1**, the *trans* orientation in **1b** must be the result of kinetic effects during the addition of the phosphines to **2**, which we explain as follows. First, addition of diphenylphosphine to **2** gives the monoadduct **6** which will adopt the half chair conformation with the diphenylphosphino group in equatorial position (Scheme 4).

The second Michael addition on **6** will proceed via the transition state **7** to furnish the enolate **8** which on protonation gives the final product **1** (an anionic mechanism is depicted, but the stereochemical arguments are equally valid for a proton catalyzed reaction). Approach of the phosphide anion to the double bond of **6** may occur from below to furnish **7a** and hence eventually **1a**, or from above which leads via **7b** to **1b**. As indicated in Scheme 4, **7a** is less favorable due to repulsion between the diphenylphosphino group and the quasi-axial methyl group; unfavorable

interactions are much less severe in the transition state **7b**. Moreover, **7a** leads to the enolate adduct **8a** which is forced to initially adopt a half boat conformation, whereas **7b** leads to the slightly more favorable half chair of **8b**. All these factors apparently combine to make **8b** and hence **1b** the kinetically favored product.

In order to convert **1b** to **1a**, we envisaged oxidation of **1b** to the corresponding bisphosphinyl derivative **5** (Scheme 2), followed by treatment with base and reduction to **1**. Oxidation of **1b** with hydrogen peroxide in dichloromethane gave **5** in nearly quantitative yield. The NMR spectral data of **5** were completely analogous to those of **1b** in the sense that there was one phosphorus signal (δ=33.1 ppm) and one type of methyl group (δ=29.1 ppm, dd, ^3J(CP)= 4 Hz, ^3J(CP)>1 Hz), which indicates that the product was **5b**, analogous to **1b**, and that, not surprisingly, the *trans* relation between the two phosphorus substituents was not affected at this stage.

Unfortunately, attempts to achieve epimerization of **5b** to **5a** were not successful. On treatment of a colorless solution of **5b** in ethanol with sodium ethoxide, a yellow solution was obtained which showed several signals in the ^{31}P NMR spectrum around δ=33 ppm; on working up, complicated ^{1}H and ^{13}C NMR spectra indicated the formation of a mixture from which pure products could not be isolated. Presumably, aldol and/or Wittig–Horner type reactions caused partial decomposition.

3. Conclusion

Our initial goal to synthesize the 1,3-diphosphine **1** was achieved only in so far as a compound was obtained with the envisaged overall structure, but unfortunately, it turned out to be **1b** with *trans* arrangement of the two phosphorus functionalities. While this stereochemistry makes **1b** unsuitable for chelate interaction with transition metals, the interpretation of the course of events gave rewarding mechanistic insights.

Simple and highly efficient means to construct chelating ligands with extra functionality remain an important goal. The formation of P–C bonds using known or perhaps novel schemes is certainly worthy of more attention. However, good catalysis requires the combination of the proper steric and electronic effects and, as we have experienced in the present case, not every *efficient* route to diphosphine ligands achieves *both* in one reaction step; stereochemistry can be of primary importance.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker WM250, a Bruker AC200 or a Bruker MSL400 spectrometer. The assignment of NMR signals is based on HH-COSY, CH-correlation, and NOE experiments. MS and HRMS spectra were recorded on a Finnigan MAT-90 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Mattson Instruments 6030 Galaxy Series FT-IR spectrometer. All chemicals used were commercially available from either Acros or Aldrich Chemicals.

4.1.1. 3,5-Bis(diphenylphosphino)-4,4-dimethylcyclohexanone (1). A mixture of 4,4-dimethyl-2,5-cyclohexadienone (**2**) (2.65 g, 21.68 mmol) and diphenylphosphine (8.07 g, 43.36 mmol) was heated under an N_2 atmosphere during 10 h at 130–135°C. The reaction mixture was cooled to room temperature; it was a yellowish homogeneous viscous oil. After addition of Et_2O (2 mL), it crystallized completely. Additional Et_2O (10 mL) was added. Because of the limited solubility of **1** in Et_2O, this suspension was cooled; **1** was filtered off under an N_2 atmosphere and washed several times with cold Et_2O to give colorless crystals of pure **1**, mp 139–140°C. The filtrate was concentrated in vacuo and additional 1.20 g of **1** were filtered off. Total yield of **1** was 8.24 g (76.9%). IR (KBr): ν 1707 (C═O), 1584 (Ph), 1476 (Ph), 1433, 743 (Ph), 700 (Ph). ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 6H, CH_3), 2.12 (dddd, 2H, ^3J(PH)=8.7 Hz, $^2J(H(2)_{anti}H(2)_{syn}$=16.7 Hz, ^3J(H(2)H(3))= 5.1 Hz, ^4J(PH)=1.2 Hz, CH_2), 2.33 (dddd, 2H, ^3J(PH)= 5.7 Hz, $^2J(H(2)_{anti}H(2)_{syn})$=16.7 Hz, ^3J(H(2)H(3))=9.4 Hz, ^4J(PH)=1.2 Hz, CH_2), 3.16 ppm (ddd, ^3J(H(2)H(3))= 9.4 Hz, ^3J(H(2)H(3))=5.1 Hz, ^2J(PH(3))=3.6 Hz, 2H, CH), 7.27–7.57 (m, 20H, 4Ph). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 27.7 (dd, ^3J(PC)=12.9 Hz, ^3J(PC)=9.1 Hz, $2CH_3$), 38.1 (t, ^2J(PC)=15.5 Hz, *C*CH_3), 40.7 (d, ^2J(PC)=3.7 Hz, $2CH_2$), 42.2 (dd, ^1J(PC)=21.6 Hz, ^3J(PC)=7.5 Hz, 2CH), 128.3–137.9 (m, 4Ph), 209.7 (t, ^3J(PC)=2.7 Hz, C═O). ^{31}P NMR ($CDCl_3$): δ −11.3. MS: *m*/*z* 494 (M^+, 5), 417 (M^+-Ph, 8), 370 (5), 309 (M^+-Ph_2P, 46), 280 (80), 265 (100), 213 (31), 186 (Ph_2PH, 90), 108 (PhP, 100). HRMS ($C_{32}H_{32}P_2O$), calc 494.1930, observed 494.1928. Anal. calcd for $C_{32}H_{32}P_2O$: C, 77.72; H, 6.52; P, 12.53. Found: C, 76.58, H, 6.56, P, 12.45.

4.1.2. 4,4-Dimethyl-3,5-bis(diphenylphosphinyl)-cyclohexanone (5). Compound **1** (0.070 g, 0.14 mmol) was dissolved in CH_2Cl_2 (7 mL) and H_2O_2 (35%, two drops) was added under stirring at ambient temperature. After 10 min, $FeSO_4$ was added to destroy an excess of H_2O_2. The reaction mixture was dried over $MgSO_4$. The solvent was evaporated in vacuo to give a colorless viscous oil, which formed a colorless precipitate on addition of Et_2O. The precipitate was filtered off to give **5** (0.073 g, 98%); it was purified by dissolving it in CH_3CN (1 mL) and precipitating with Et_2O. **5**: colorless crystals, mp 121–122°C. IR (KBr): ν 1715 (C═O), 1591, 1483, 1439, 1179, 1113, 700, 519. ^{1}H NMR ($CDCl_3$): δ 1.14 (s, 6H, CH_3), 2.47 (ddd, 1H, ^3J(PH)=16.0 Hz, $^2J(H(2)_{anti}H(2)_{syn})$=16.8 Hz, ^3J(H(2)H(3))=6.3 Hz, CH*H*), 2.56 (ddd, 1H, ^3J(PH)= 11.8 Hz, $^2J(H(2)_{anti}H(2)_{syn})$=16.8 Hz, ^3J(H(2)H(3))= 8.2 Hz, C*H*H), 3.62 (dddd, 1H, ^2J(PH)=6.6 Hz, ^4J(PH)= 2.3 Hz, ^3J(H(2)H(3))=8.2 Hz, ^3J(H(2)H(3))=6.3 Hz, CH), 7.19–7.95 (m, 20H, Ph). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 28.7 (dd, ^3J(PC)=4.0 Hz, ^3J(PC)>1 Hz, $2CH_3$), 37.9 (s, $2CH_2$), 39.4 (t, ^2J(PC)=3.1 Hz, *C*$(CH_3)_2$), 42.2 (dd, ^1J(PC)= 68.5 Hz, ^3J(PC)=7.1 Hz, 2CH), 128.4–135.2 (m, 4Ph), 206.7 (t, ^3J(PC)=17.6 Hz, C═O). ^{31}P NMR ($CDCl_3$): δ 33.1. MS: *m*/*z* 526 (M^+, 8), 498 (12), 325 (M^+-Ph_2PO, 18), 270 (51), 201 (Ph_2PO, 100), 183 (13), 77 (Ph, 31). HRMS ($C_{32}H_{32}P_2O_3$), calc 526.1823, observed 526.1827.

Anal. calcd for $C_{32}H_{32}P_2O_3$: C, 72.99; H, 6.13; P, 11.77. Found: C, 70.30, H, 6.28, P, 11.30.

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