Synthesis of Phosphine−Rhodium Complexes Attached to a Standard Peptide Synthesis Resin

Scott R. Gilbertson,* Xifang Wang, Garrett S. Hoge, Christopher A. Klug,† and Jacob Schaefer

Department of Chemistry, Washington University, St. Louis, Missouri 63130

Received July 18, 1996[⊗]

Summary: Solid-phase peptide synthesis was used to synthesize polymer-supported, peptide-based bis(phosphine sulfides). Chemistry was developed that allows for the conversion of the phosphine sulfides to phosphines while they remain attached to the support resin. The transformation of protected phosphine to phosphine to metal complex was followed by solid-state ^{31}P NMR. The resin-supported rhodium complexes were used in the hydrogenation of olefins.

We recently reported a method that allows for the synthesis of phosphine-containing peptides.[1−3] One of the initial goals of that work was to position transition metals into stable predictable peptide structural motifs and use that situation to control the selectivity of catalytic reactions performed by the transition metal. A second advantage of a peptide-based approach to phosphine design is the ability to synthesize a wide variety of structurally unique phosphine ligands by synthesizing a number of peptides. The ultimate extension of this approach would be the synthesis of new phosphine ligands by combinatorial methods. Before this task could be undertaken, a major problem had to be overcome. Our initial chemistry utilized phosphine sulfides as a method for the protection of phosphines from oxidation to their phosphine oxides during solid-phase peptide synthesis.[1,2] After synthesis and purification, reduction of the phosphine sulfides to phosphines yielded a ligand capable of binding catalytically useful transition metals. The reductant used in this system was Raney nickel. While this chemistry worked well on single soluble phosphine ligands, it quickly became clear that this method was not practical for the simultaneous reduction of the large numbers of ligands that would be generated by a combinatorial approach. To facilitate isolation and screening of our ligands, we also desired to form the metal complexes while the ligands were attached to the synthesis support. The reduction of phosphine sulfides back to phosphines with the heterogeneous Raney nickel was clearly ill suited for this task. This paper reports a homogeneous reagent system that allows for the reduction of peptide-based phosphine sulfides while they are attached to the polymer support they were synthesized on. The metalation of a sample system attached to polystyrene, along with the catalysis of the hydrogenation of an olefin, is also reported. The reaction sequence of ligand precursor to polymer-supported ligand to the polymer-supported ligand−metal complex was followed by solid-state ^{31}P NMR.

Beyond the area of combinatorial synthesis of new phosphine ligands, the chemistry reported in this paper has application in the area of polymer-bound transition-metal catalysts. A wide variety of metal-ligand systems have been incorporated into polymers, with metal−phosphine complexes being one of the most studied.[4−12] The synthesis of well-defined polymer phosphine systems requires the ability to make controlled chemical modifications. The use of phosphine sulfides as phosphine synthons greatly increases the arsenal available to chemists interested in this problem. Using the chemistry reported in this paper phosphine sulfide containing polymers can be synthesized, manipulated, and purified in air without oxidation to the phosphine oxide. Reduction of the sulfide to the free phosphine can then be used to generate ligands ready for metalation and catalysis.

The peptide synthesized was a 12-residue peptide, (Ac-Ala-Aib-Ala-Pps(S)-Ala-Ala-Aib-Cps(S)-Ala-Ala-Aib-Ala-polymer) (**1**), containing amino isobutryic acid to increase secondary structure. Assuming the peptide would have an α-helical secondary structure,[13−16] the phosphine-containing amino acids were positioned in an i and i+4 orientation to each other. This would place the metal binding groups on the same side of an α-helical peptide. The peptide was synthesized by standard solid-phase peptide synthesis methods,[17] using phosphine-containing amino acids where the phosphine is protected as the phosphine sulfide.[1−3] The critical step in the sequence was the conversion of the phosphine sulfide to a phosphine while the peptide remained attached to the polystyrene support it was synthesized

† Present address: Department of Chemical Engineering, Stanford University, Stanford, CA 94305.

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

(1) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481.
(2) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434.
(3) Gilbertson, S. R.; Pawlick, R. V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 902.
(4) Allum, K. G.; Hancock, R. D.; Howell, I. V.; Pitkethly, R. C.; Robinson, P. J. *J. Organomet. Chem.* **1975**, *87*, 189.
(5) Brown, J. M.; Molinari, H. *Tetrahedron Lett.* **1979**, 2933.
(6) Dumont, W.; Poulin, J. C.; Dang, T. P.; Kagan, H. B. *J. Am. Chem. Soc.* **1973**, *95*, 8295.
(7) Evans, G. O.; Pittman, C. U.; McMillan, R.; Beach, R. T.; Jones, R. *J. Organomet. Chem.* **1974**, *67*, 295.
(8) Grubbs, R. H.; Kroll, L. C.; Sweet, E. M. *J. Macromol. Sci.-Chem.* **1973**, *7*, 1047.
(9) Pittman, C. U.; Hirao, A. *J. Org. Chem.* **1978**, *43*, 640.
(10) Takaishi, N.; Imai, H.; Bertelo, C. A.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5400.
(11) Fritz, H. P.; Blümel, J.; Dengler, D. *Z. Naturforsch., B* **1993**, *48*, 1589.
(12) Ro, K. S.; Woo, S. I. *Appl. Catal.* **1991**, *69*, 169.
(13) Stewart, J. M. *Amphipathic Helixes in Designed Peptide Structures*; CRC Press: Boca Raton, FL, 1993.
(14) Ghadiri, M. R.; Soares, C.; Choi, C. *J. Am. Chem. Soc.* **1992**, *114*, 825.
(15) Karle, I. L.; Balaram, P. *Biochemistry* **1990**, *29*, 6748.
(16) Schulz, G. E.; Schirmer, R. H. *Principles of Protein Structure*; Springer-Verlag: New York, 1988.
(17) Peptide synthesis was done with a DuPont RaMPS Multiple Peptide Synthesis System.

S0276-7333(96)00600-0 CCC: $12.00

on.[18] Methylation of the phosphine sulfide **1** with methyl trifluoromethanesulfonate gave the phosphonium salt **2**. Treatment of this salt with tris(dimethylamino)phosphine resulted in removal of the sulfur, giving bis(phosphine) **3** and a (methylthio)(dimethylamino)phosphonium salt as the products.[18] The (methylthio)(dimethylamino)phosphonium salt was then washed away from the polymer-bound phosphines. Treatment of the bound bis(phosphine) with the cationic rhodium species $[Rh(NBD)^{+}\ ^{-}\ ClO_4]$ gave the desired rhodium complex **4**. Initially, this reaction was followed by the change in the resin to the typical yellow color of rhodium phosphine complexes.

The conversion of the phosphine sulfide containing peptide to a phosphine−metal complex is critical for the success of this chemistry. Solid-state ^{31}P NMR proved to be an ideal method for monitoring this reaction *in situ*.[19−23] Reaction of the phosphine sulfide (Figure 1, top) with methyl trifluoromethanesulfonate followed by reaction of the bis(phosphonium) salt with tris(dimethylamino)phosphine causes the two major resonances of the phosphine sulfide to shift to two overlapping resonances at −20 ppm (Figure 1, middle). Peaks due to incomplete reaction with tris(dimethylamino)phosphine are also present as well as a peak that corresponds to the (methylthio)tris(dimethylamino)phosphonium salt. The polymer-bound bis(phosphine) was treated with less than 1 equiv of $[Rh(NBD)^{+}\ ^{-}\ ClO_4]$, resulting in the decrease in the resonance at −20 ppm and a peak appearing at 30 ppm due to the metal complex[24] (Figure 1, bottom). The use of excess rhodium was avoided to prevent coordination of the metal to other functional groups in the peptide.

The representation of the peptide in Scheme 1 assumes a helical structure and binding of the metal between two phosphines that are attached to the same peptide backbone. At this time we do not absolutely know that this is the case. It is certainly possible that the peptide does not have a helical secondary structure and that the metal is bound between two different peptide chains. It is quite likely that both of these modes of chelation exist in this system. We are currently looking at different densities of loading on the synthesis polymer to determine how a decrease in local concentration affects the chemistry and spectroscopy we observe. We are also looking at the metal binding and the catalytic properties of systems with mono(phosphine)-containing peptide chains.

After determining by solid-state NMR that the complex had formed, we tested the polymer-bound rhodium complex to determine if it was a viable catalyst system. The resin was prepared in the same manner as for the solid-phase NMR. Further, after coordination of the rhodium the resin was washed six times with three portions each of methanol and dimethylformamide, followed by three additional methanol washings. These efforts were taken to ensure that any catalysis observed was the result of phosphine-bound rhodium. The reaction initially chosen was the hydrogenation of the prochiral enamide (**6**). The reactions were run at 150 psi of H_2, using an orbital shaker for stirring. After each reaction the polystyrene beads were removed by filtration and used to catalyze the reaction again. The support-bound catalyst was recycled six times without a qualitative loss of activity. As a control, a peptide without phosphine-containing amino acids was synthesized, [Ac-Ala-Aib-Ala-Ala-Ala-Ala-Aib-Ala-Ala-Ala-Aib-Ala-polymer] (**8**). Peptide **8** was treated with $[Rh(NBD)^{+}\ ^{-}\ ClO_4]$ by exactly the same procedure as peptide **1**. This peptide did not take up the yellow color

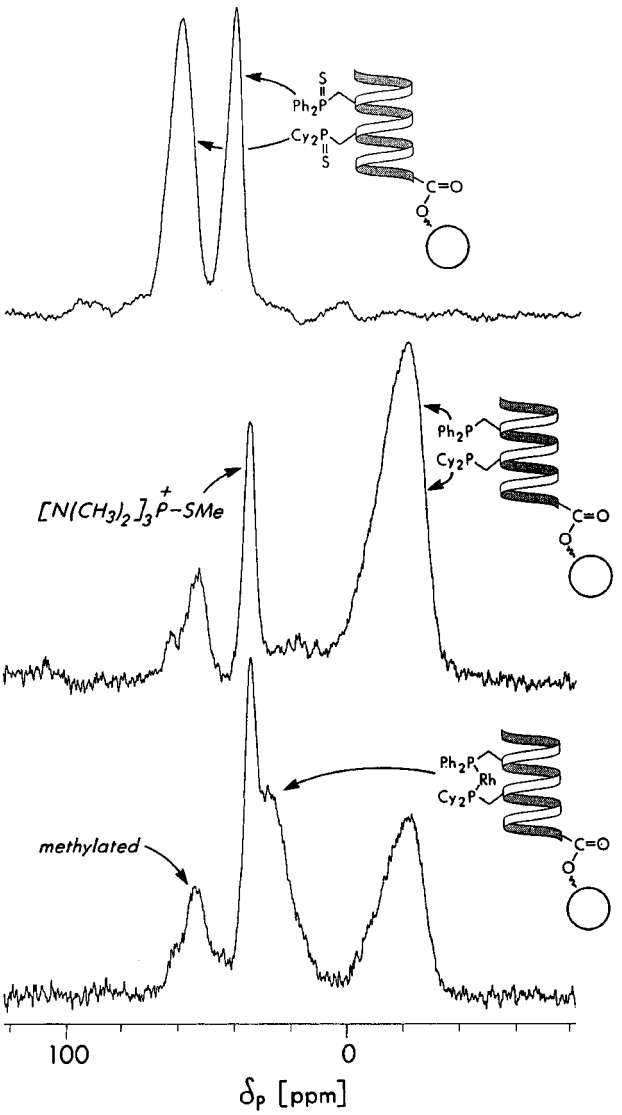
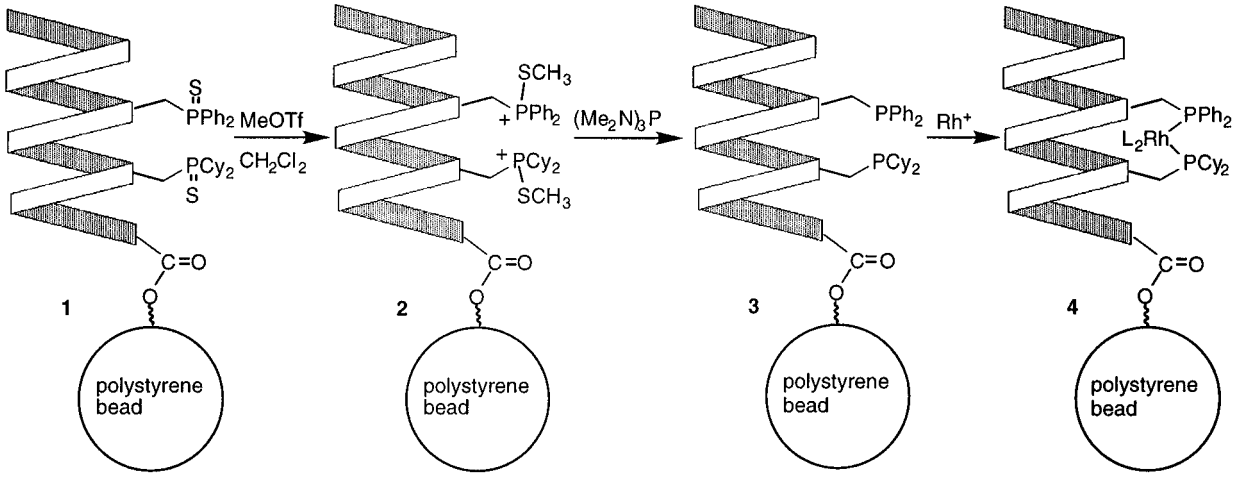


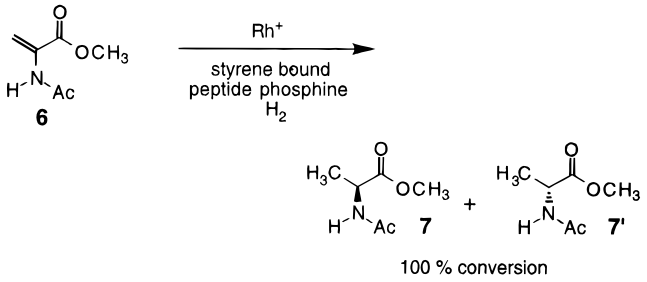
Figure 1. Cross-polarization, magic-angle spinning 121-MHz ^{31}P NMR spectra of a phosphine sulfide substituted peptide attached to a polystyrene resin (top) and of the products after conversion of the phosphine sulfides to phosphines (middle) and after complexation of the phosphines to rhodium (bottom). Additional peaks are due to methylated starting materials and incomplete reaction. All phosphorus starting materials, products, and intermediates are attached to the resin. Spectra were obtained with 5 kHz magic-angle spinning and total suppression of sidebands. The chemical shift scale is referenced to external phosphoric acid (0 ppm).

(18) Omelanczuk, J.; Mikolajczyk, M. *Tetrahedron Lett.* **1984**, *25*, 2493.
(19) Fyfe, C. A.; Clark, H. C.; Davies, J. A.; Hayes, P. J.; Wasylishen, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 6577.
(20) Clark, H. C.; Fyfe, C. A.; Hayes, P. J.; McMahon, I. *J. Organomet. Chem.* **1987**, *322*, 393.
(21) Lindner, E.; Schreiber, R.; Kemmler, M.; Schneller, T.; Mayer, H. A. *Chem. Mater.* **1995**, *7*, 951.
(22) Lindner, E.; Kemmler, M.; Schneller, T.; Mayer, H. A. *Inorg. Chem.* **1995**, *34*, 5489.
(23) Dixon, W. T. *J. Chem. Phys.* **1982**, *77*, 1800.
(24) The ^{31}P solid-state NMR chemical shifts all agree with the corresponding chemical shifts obtained for the soluble phosphine-containing peptide in solution.

Scheme 1



Scheme 2



characteristic of a rhodium complex and did not catalyze the hydrogenation of enamide **6**. This is evidence that the catalysis observed with peptide **1** is due to the phosphine−metal complex and not free rhodium or rhodium complexed to other groups on the peptide.

Given that the metal was attached to the polystyrene via a 12-residue peptide which not only contained nine chiral centers but also had the potential to adopt a well-defined secondary structure, we were interested in the amount of asymmetric induction obtained with this catalyst. While the eventual goal is to use this type of system in the development of selective catalysts, selectivity was not considered when the peptide sequence for this initial attempt was designed. The reaction was found to yield the protected amino acids in 4−9% enantiomeric excess.

This paper reports an approach that allows for the rapid and clean conversion of polymer-bound phosphine sulfides to free phosphines. This chemistry is critical for the implementation of phosphine sulfide building blocks in the synthesis of libraries of ligands by combinatorial methods. This chemistry will greatly enhance the ability to synthesize new types of phosphine complexes that can then be designed to exhibit a variety of types of catalytic activity. Along with the obvious application in combinatorial chemistry this chemistry, increases the accessibility of polymer-bound phosphine ligands in general.

Acknowledgment. We gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH Grant No. 1S10R02004, and the Washington University Mass Spectrometry Resource Center, partially supported by NIH Grant No. NIHRR00954, for their assistance. This work was also partially supported by NIH Grant No. GM51554.

Supporting Information Available: Text and a table giving synthetic details and NMR data for the complexes prepared in this paper (3 pages). Ordering information is given on any current masthead page.

OM9606000