Synthesis of (Dicyclohexylphosphino)serine, Its Incorporation into a Dodecapeptide, and the Coordination of Rhodium

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The coordination of metals to peptides has a number of applications. Metal binding has been used to stabilize and control peptide structure.[1−8] The incorporation of metal binding sites into proteins can facilitate protein purification or control of enzyme activity.[9,10] Metal−protein conjugates can deliver medicinally important metals for imaging.[11,12] The majority of the metal-ligating groups placed in peptides contain oxygen and nitrogen.[13] The chemistry of coordination complexes of this type is rich, but there is a wide variety of transition metal chemistry that is not accessible to this type of complex. For example, transition metal complexes useful for effecting hydrogenation,[14] hydroformylation,[15] and π-allylpalladium[16,17] reactions are often phosphine based and hence not normally associated with biologically based ligands. For this reason, we embarked on the development of amino acids that contain phosphine ligands. With a variety of phosphine amino acids available, one should be able to build protein-metal conjugates with metals such as rhodium, ruthenium, palladium, and platinum. These conjugates could, in turn, be used to capitalize on both the metal's ability to influence peptide conformation as well as the peptide's ability to potentially control metal reactivity by placing the metal in unique steric environments. In addition, the use of a peptide-based framework for a metal should allow for the synthesis of diphosphine ligands where the electronic properties of the two phosphines are different.[18,19] In the past, the use of electronically different phosphines with small ligands has been limited by the need for C_2 symmetry.[20] Because peptide-based phosphine ligands should exist in one conformation, they offer a unique opportunity to take advantage of diphos-ligands with two phosphines that are electronically different. This paper reports the synthesis of a new phosphine amino acid precursor, (dicyclohexylphosphino)-serine sulfide (**1**), which can be converted to the phosphine (**2**) (Cps) (Figure 1).[21] This amino acid (**1**) was incorporated into a 12-residue peptide along with another phosphine derivative of serine [(diphenylphosphino)-serine (Pps)].[22] After synthesis of the peptide, the phosphine sulfides were converted to the corresponding phosphines and rhodium was coordinated to the peptide.

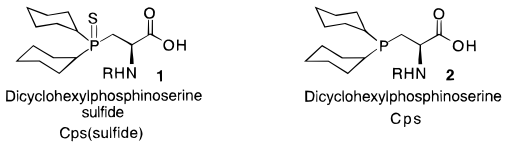
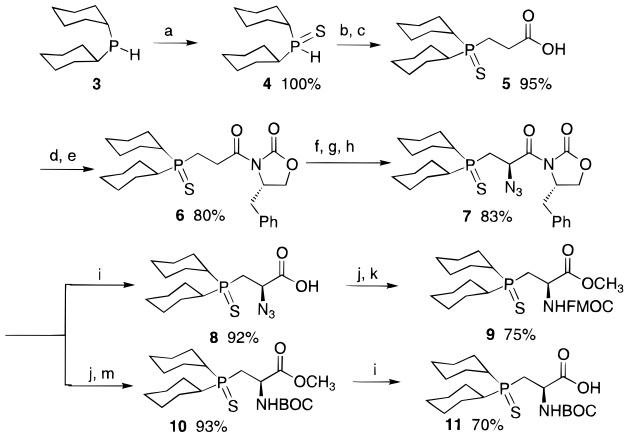


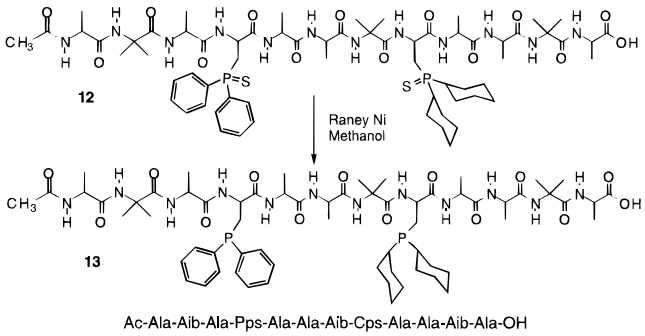
Figure 1.

Scheme 1[a]



[a] Key: (a) S_8, 1/8 equiv of C_6H_6, rt, 2 h; (b) nBuLi, 1.0 equiv, THF, −78 °C; (c) acrylic acid, 0.5 equiv, −78 °C to rt; (d) ClC(O)OtBu, THF, −78 to 0 °C, 1.5 h; (e) (*S*)-(−)-lithium, 4-benzyl-2-oxazolidinone, THF, −78 to 0 °C, 2 h; (f) KHMDS, THF, −78 °C, 30 min; (g) Tris−N_3, THF, −78 °C, 5 min; (h) HOAc, −78 to 0 °C, 8 h; (i) LiOH, THF/H_2O, 0 °C; (j) $SnCl_2$, MeOH, 24 h; (l) FmocOSU, $NaHCO_3$, acetone/H_2O; (m) $(BOC)_2O$, $NaHCO_3$, dioxane/H_2O.

Scheme 2



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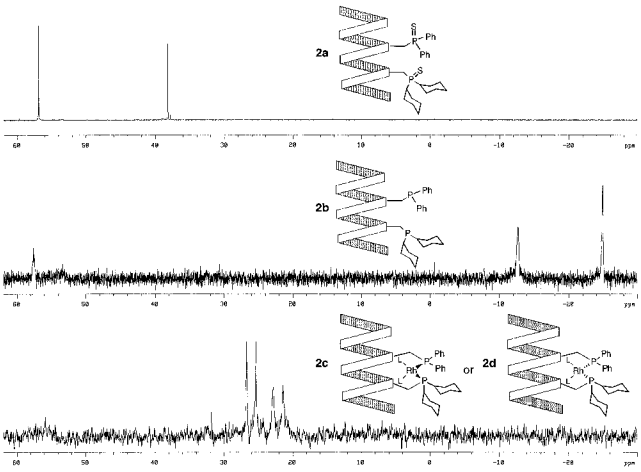

Figure 2. Ac-Ala-Aib-Ala-Pps-Ala-Ala-Aib-Cps-Ala-Alqa-Aib-Ala-OH.

The dodecapeptide synthesized here represents the first example of a peptide-based diphos ligand with electronically different phosphines.

The first step in the synthesis of the dicyclohexylphosphinoserine was a conjugate addition of the anion of dicyclohexylphosphine sulfide (**4**) to acrylic acid. After difficulty was experienced with the addition of the dicyclohexylphosphide anion, this proved to be an excellent route to the desired phosphine sulfide (**5**).

We have synthesized both FMOC and tBOC protected amino acids. The phosphine sulfide acid was first converted to the α-azide (**7**) using chemistry developed by Evans (Scheme 1).[23−25] This compound (**7**) was the branch point in the synthesis of the FMOC- and tBOC-protected amino acids. Reaction of the azide oxazolidone (**7**) with lithium hydroxide gave the azide acid (**8**). Reduction of the azide with tin(II) chloride in methanol afforded the amino methyl ester which was then protected as the FMOC carbamate to give **9**. The tBOC-protected amino acid (**11**) was synthesized by reduction of the azide oxazolidone (**7**) with tin(II) chloride followed by tBOC protection of the amine with *tert*-butyl anhydride. Hydrolysis of **10** with lithium hydroxide then gave the acid (**11**) ready for peptide coupling.

To demonstrate that this phosphine-containing amino acid was compatible with solid phase peptide synthesis methods, we have incorporated it into a 12-residue peptide (**13**) (Scheme 2).

The peptide chosen was designed to be soluble in organic solvents and have high helix content. The two phosphine-containing amino acids were positioned with three residues between them to allow for the proper orientation for metal coordination assuming an α-helical secondary structure. The peptide was synthesized by standard FMOC chemistry on polystyrene resin.

The desulfurization and metalation reactions were easily followed by ^{31}P NMR.[26] Figure 2a is the ^{31}P spectra of the diphosphine sulfide. Upon reaction with Raney nickel, the ^{31}P chemical shifts moved upfield to the appropriate range for phosphines (Figure 2b). Reaction with $RhCl(NBD)^+$ $^-ClO_4$ gave the cationic rhodium-containing peptide. Upon complexation of rhodium, the ^{31}P resonances shift downfield and coupling between spin 1/2 ^{103}Rh and the phosphines was observed (Figure 2c).

This ligand has the potential to exist in two different conformations (Figure 2c,d), one in which the metal points out of the page (Figure 2c) and one in which the metal points back into the plane of the paper (Figure 2d). Control of this type of conformation is difficult in the case of small molecules and is generally overcome through the use of C_2 symmetric ligands. Since the peptide phosphine ligands are not C_2 symmetric, it is essential that the metal complex exist in one conformation. As can be seen in Figure 2, there is one set of ^{31}P resonances for the peptide. This means the peptide is either in one conformation or is in rapid equilibrium between different conformations. We have tested this by variable-temperature NMR. The ^{1}H and ^{31}P NMR spectra of this complex do not change over the temperature range of −40 to +40 °C. This indicates that the complex probably exists in one conformation. We are currently attempting to determine which conformation exists by looking for dipolar exchange between the protons in the backbone of the peptide and the phenyl rings on the phosphines.

As stated earlier, one of the major goals of this work is to ultimately develop new selective catalysts. We have taken a preliminary look at the activity of the rhodium−phosphine complex. We have found the reactivity of this complex, in hydrogenation to be qualitatively the same as simple DIPHOS−rhodium complexes. The hydrogenation of methyl 2-acetamidoacrylate with this catalyst gives *N*-acyl alanine methyl ester in high yield and 8% ee. While the enantiomeric excess is low, the inital goal was to determine if this type of complex was capable of performing catalytic chemistry. Positioning rhodium in a peptide places the metal in the vicinity of both amide nitrogens and carbonyls. Either of these potential ligands could have coordinated to the rhodium and interrupted the catalytic cycle. This apparently is not a problem, since the metal ligand system turns over readily. Now that we have established that these complexes catalyze hydrogenation we are building a series of peptides with (diphenylphosphino)serine and (dicyclohexylphosphino)-serine in different positions along the peptide backbone. This will enable us to evaluate a number of different environments for transition metals.

The ability to incorporate phosphines into various peptide structures allows for the facile synthesis of a wide variety of phosphine ligands. In principle, a large number of such ligands can be synthesized and screened for unique structural characteristics, useful reactivity, or important biological activity. We are currently using commercially available technology to build such libraries of ligands.

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Supporting Information Available: Complete experimental and spectroscopic data for all described compounds (10 pages).

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