Palladium-Catalyzed Synthesis of Phosphine-Containing Amino Acids

Scott R. Gilbertson* and Gale W. Starkey

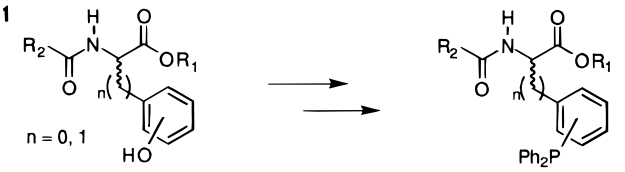
Department of Chemistry, Washington University, Campus Box 1134, St. Louis, Missouri 63130-4899

Received January 12, 1996 (Revised Manuscript Received February 22, 1996)

The use of phosphine ligands in organometallic chemistry is ubiquitous.[1,2] Phosphine metal complexes have been used in applications from catalysis[3−7] to chelation of metals for medical imaging.[8−11] For some time we have been interested in the synthesis of new chiral phosphines based on the utilization of biological structures. As a consequence, we are attempting to develop new routes to highly functionalized phosphines. One of the severe limitations on the chemistry of phosphine ligands is the difficulty of their synthesis. Most phosphines are synthesized by either addition of a Grignard or organolithium reagent to a phosphine chloride or reaction of phosphide anion with an electrophile.[12,13] Both of these routes are incompatible with sensitive functionality, particularly base-sensitive groups. The phosphide anion is often sufficiently nucleophilic to react with typical organic protecting groups, particularlly ethers and esters. To facilitate the synthesis of phosphines containing complicated functionality, especially protected amino acids, we have developed a catalytic method for the conversion of phenols to arylphosphines (Scheme 1). To demonstrate the utility of this reaction, we have used this chemistry to convert derivatives of tyrosine to phosphines. This chemistry has also been used to convert the phenolic hydroxyl of a tyrosine-containing peptide to a phosphine group.

In 1987, Stille reported the palladium-catalyzed reaction of aryl halides with (trimethylstannyl)diphenylphosphine and (trimethylsilyl)diphenylphosphine.[14] The Stille coupling provides a mild method for the formation of a wide variety of arylphosphines. As part of a larger project, in which we are interested in synthesizing peptides that contain phosphines in their side chains, a transformation that appealed to us was conversion of the OH of tyrosine to a phosphine. We felt that given the Stille precedent, along with the fact that palladium-catalyzed couplings with aryl and vinyl triflates are well

Scheme 1



known,[15] one should be able to convert the OH of tyrosine to a phosphine by proceeding through the aryl triflate. Recently, a group from Merck Process Research has reported this transformation using nickel catalysis.[16] Cai et al. have developed a practical method for the conversion of dinaphthol to BINAP without racemization of the sensitive starting diphenol.

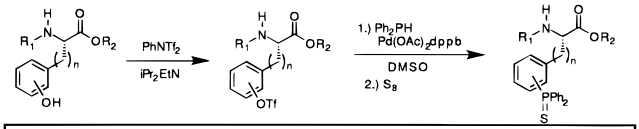
Independent of the Merck group, we have developed a palladium-catalyzed version of the reaction. Conversion of the protected amino acids to their triflates was performed by the method of McMurry and Scott.[17−19] Reaction with *N*-phenyltrifluoromethanesulfonamide and diisopropylethylamine gives good to excellent yields of the required aryl triflates (Table 1). Stille's procedure to convert aryl halides to phosphines uses (trimethylstannyl)diphenylphosphine as the source of phosphine. Our attempts to use this reagent under palladium catalysis with aryl triflates resulted in no reaction. We found that readily available diphenylphosphine is an acceptable source of phosphorus for our reaction. Initially, it was found that *N*-acyltyrosine could be converted to its triflate. Reaction of the triflate with diphenylphosphine and $Pd(OAc)_2$ in the presence of dppb gave the phosphine amino acid in good yield, albeit with racemization of the α-carbon. As expected, racemization of the amino acid α-carbon is sensitive to the protecting group on the amine. Replacement of the acetate with *t*-Boc allows the reaction to be run without racemization. As an example, reaction of diphenylphosphine and the triflate of *N*-tBoc-L-tyrosine benzyl ester with palladium under our conditions gave a good yield of the corresponding phosphine, without racemization at the α carbon (Table 1, entry 2).[20] This reaction also proceeds with the ortho and meta isomers of tyrosine, as well as with hydroxylphenylglycine to give new phosphine ligands (Table 1).

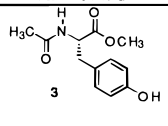
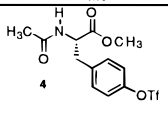
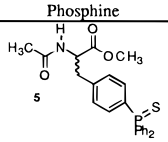
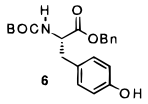
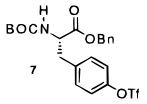
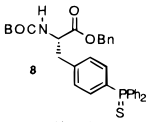
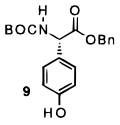
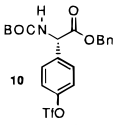
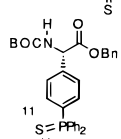
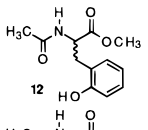
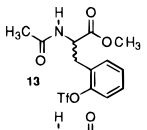
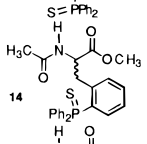
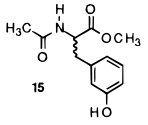
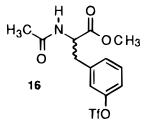
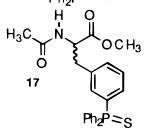
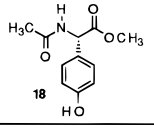
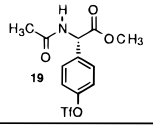
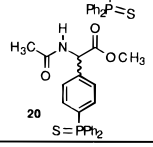
There appear to be distinct differences between this system and the Merck method. The Merck group reported that the use of palladium under their conditions gave no reaction. One explanation for the difference in reactivity is the use of DMSO as the solvent in our system. It is not known if the effect of DMSO is intrinsic to the solvent or simply due to the ability of run the reaction at a higher temperature in DMSO. We also found the reaction does not take place in DMF with palladium. The potential issue of oxidation of the metal species in the catalytic cycle by DMSO does not appear to be a problem.[21,22] In our hands, the Nickel system

(1) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(2) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(3) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.
(4) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901.
(5) Noyori, R.; Kitamura, M. *Enantioselective Catalysis with Metal Complexes an Overview*; Springer Verlag: New York, 1989; Vol. 5.
(6) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
(7) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183.
(8) Katti, K. V.; Volkert, W. A.; Ketring, A. R.; Singh, P. R. US Patent No. WO 93/08839, 1993.
(9) Abrams, M. J.; Larsen, S. K.; Shaikh, S. N.; Zubieta, J. *Inorg. Chim. Acta* **1991**, *185*, 7.
(10) Deutsch, E.; Libson, K.; Becker, C. B.; Francis, M. D.; Tofe, A. J.; Ferguson, D. L.; McCreary, L. D. *J. Nucl. Med.* **1980**, *21*, 859.
(11) Deutsch, E.; Libson, K. *Comments Inorg. Chem.* **1984**, *3*, 83.
(12) *Organophosphorous Chemistry*; The Royal Chemical Society: London, 1969−1983; Vols. 1−15.
(13) Kosolapoff, G. M.; Maier, L., Eds. *Organic Phosphorus Compounds*, 2nd ed.; Wiley-Interscience: New York, 1972; Vol. 1.
(14) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748.
(15) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.
(16) Cai, D.; Payack, J. F.; Bender, D. R.; Hyghes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.
(17) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(18) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.
(19) Petrakis, K. S.; Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831.
(20) The optical purity of the amino acid was determined by coupling to optically active alanine and determining the ratio of diastereomers.
(21) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*.

S0022-3263(96)00077-1 CCC: $12.00

Table 1. Synthesis of Amino Acid Triflates and Phosphine Ligands



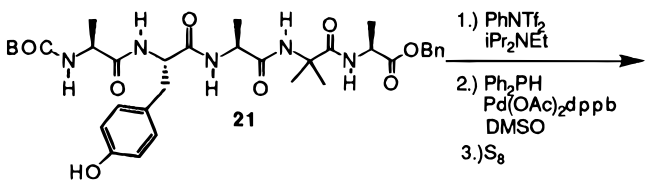
	Amino Acid	Triflate	Yield	Phosphine	Yield
1	 3	 4	90%	 5	89%
2	 6	 7	78%	 8	81%
3	 9	 10	35%	 11	89%
4	 12	 13	98%	 14	94%
5	 15	 16	81%	 17	72%
6	 18	 19	87%	 20	93%

results in cleavage of the acid protecting group along with formation of the phosphine product.

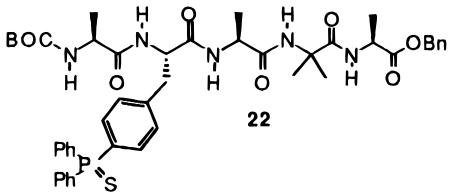
The phosphine amino acids were reacted with elemental sulfur to convert the potentially air-sensitive phosphine group to a phosphine sulfide group, which is stable to chromatography in air. We have shown previously that the sulfide group is an effective protecting group for phosphines, being easily removed with Raney nickel.[23,24]

Morgans et al. have reported the reaction of aryl triflates with a variety of phosphorus species under palladium catalysis. They found reaction with diphenylphosphine oxide gives a product similar to the phosphine sulfides we ultimately obtain. There is an important functional difference between these two types of products. The conversion of phosphine oxides to phosphines is not a facile reaction. It is generally performed with silanes or hydride reducing agents. We have never been able to perform this conversion on amino acid based

Scheme 2



Boc-Ala-Tyr-Ala-Aib-Ala-OBn



phosphine oxides. We attempted the phosphine sulfide analog of the Morgans reaction. If successful, this method would have provided the phosphine sulfides directly from the aryl triflates. We found the sulfur analog of the reaction developed by Morgans yielded only recovered starting material. This is likely due to poisoning of the catalytic metal by the phosphine sulfide.

While this reaction is a convenient route to phosphine derivatives of tyrosine it also presents the possibility for the direct conversion of tyrosine residues in larger peptides to phosphine ligands. To demonstrate the feasability of this idea we have run the reaction on tyrosine-containing pentapeptide **21**. Pentapeptide **21** was treated with *N*-phenyltrifluoromethanesulfonamide and diisopropylethylamine. Reaction of the purified triflate under the standard reaction conditions discussed above gave the phosphine-containing peptide **22**, in 78% yield (Scheme 2). This reaction indicates that it may be possible to use this chemistry to convert the phenols of naturally occuring tyrosine-containing proteins to phosphines.

In conclusion, this reaction can be used to convert derivatives of tyrosine and hydroxyphenylglycine to phosphine ligands as the single amino acids or when they are present in larger peptides. We are currently using this chemistry to synthesize phosphine ligands for use in catalysis and in the development of metal binding groups for medical imaging.

Acknowledgment. We gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH 1S10R02004, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance. G.W.S. thanks Monsanto for support in the form of a graduate fellowship.

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

JO960077Z

(22) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908.
(23) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481.
(24) A detailed example of the Raney nickel reduction of a phosphine sulfide to a phosphine is included in the supporting information.