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The Combinatorial Synthesis of Chiral Phosphine Ligands

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Abstract: Chemistry is reported that allows for the synthesis and screening of phosphine ligands by standard combinatorial technology. To demonstrate the method a 63 member library of phosphine containing peptides was synthesized. Rhodium was complexed to the phosphine ligands while they were attached to the synthesis support. Each member of the library was screened for its ability to catalyze the asymmetric hydrogenation of enamide (**3**). Some correlation between specific substitutions in the primary sequence of the peptide and the highest enantiomeric excesses was observed. Copyright © 1996 Elsevier Science Ltd

Combinatorial chemistry has recently burst on the scene as a valuable tool for the discovery of new drug candidates.[1-6] The ability to synthesize hundreds of compounds for screening is a useful complement to rational drug design. There are many similarities between the design of new therapeutic agents and the development of new asymmetric ligands, the most important of which is the limitation of a rational design strategy. For this reason we have embarked on a program that will allow the use of combinatorial technology in the development of new ligands for transition metal catalyzed asymmetric reactions. This method utilizes chemistry we reported earlier for the synthesis of phosphine containing peptides.[7,8] The following paper illustrates that this chemistry is compatible with standard solid phase peptide chemistry, and allows for the incorporation of phosphine containing amino acids into virtually any peptide structure attainable by solid phase peptide chemistry. Reported here is the synthesis of, what is to our knowledge, the first library of phosphine ligands generated by combinatorial methods.[9-11] Also reported is the binding of rhodium to the phosphine ligands while they are attached to the synthesis support and a method that screens the immobilized metal complex's ability to catalyze hydrogenation of prochiral olefins.[12-20] While the enantiomeric excesses obtained for this first generation library were moderate, this paper demonstrates the potential for the use of combinatorial methods in the development of new phosphine ligands.

There are a wide variety of combinatorial methods available. Often the choice of which method to use is dependent on how the evaluation of members of the library is to be carried out. In the case of screening members of a library containing ligands for asymmetric catalysis, the screen is ultimately catalysis of a reaction. For this reason a combinatorial system was chosen that allowed the synthesis of discrete isolated compounds.[21,22] The synthesis of peptides on pins allowed us to know the identity of each peptide ligand attached to a given pin, and kept the peptides separate so screening of individual ligand metal complexes could be performed.

To facilitate the screening of each member of the library, the system was developed in such a way that catalysis could be performed while the metal complexes were still attached to the support. During the synthesis of the peptide ligands, the phosphines were protected as the phosphine sulfides. The phosphine sulfides were then converted to the free phosphines by methylation followed by treatment with HMPT.[23,24] Reaction with cationic rhodium then gave the yellow rhodium phosphine complexes attached to the solid support.

Figure 1

Figure 2 Sequences synthesized by combinatorial approach

Each peptide sequence will be

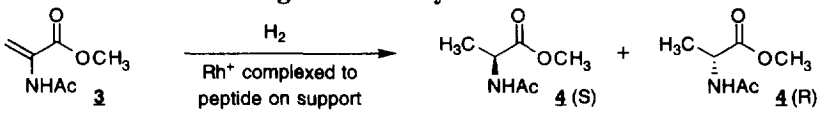
Ac-Ala-Aib-Ala-[ ]-Ala-Aid-Ala-NH_2

	i, i+4 orientation			***i, i+1 orientation***				
	Cps-Pps			**di-Pps**			***di-Pps***	
A1	-**Pps**-Ala-Ala-Aib-**Pps**-		D4	-Phe-Ala-Ala-**Pps**-**Pps**-		G4	-Phe-Ala-**Pps**-**Pps**-	
A2	-**Pps**-Ala-Ala-Phe-**Pps**-		D5	-**Pps**-**Pps**-Ala-Ala-Phe-		G5	-Val-Ala-**Pps**-**Pps**-	
A3	-**Pps**-Phe-Ala-Aib-**Pps**-		D6	-Val-Ala-Ala-**Pps**-**Pps**-		G6	-His-Ala-**Pps**-**Pps**-	
A4	-**Pps**-Ala-Ala-Val-**Pps**-		D7	-**Pps**-**Pps**-Ala-Ala-Val-		G7	-Ile-Ala-**Pps**-**Pps**-	
A5	-**Pps**-Val-Ala-Aib-**Pps**-		D8	-His-Ala-Ala-**Pps**-**Pps**-				
A6	-**Pps**-Ala-Ala-His-**Pps**-		E1	-**Pps**-**Pps**-Ala-Ala-His-			***di-Cps***	
A7	-**Pps**-His-Ala-Aib-**Pps**-	(**R**)	E2	-Ile-Ala-Ala-**Pps**-**Pps**-		G8	-Phe-Ala-**Cps**-**Cps**-	
A8	-**Pps**-Ala-Ala-Ile-**Pps**-		E3	-**Pps**-**Pps**-Ala-Ala-Ile-		H1	-Val-Ala-**Cps**-**Cps**-	
B1	-**Pps**-Ile-Ala-Aib-**Pps**-					H2	-His-Ala-**Cps**-**Cps**-	
				i, i+1 orientation		H3	-Ile-Ala-**Cps**-**Cps**-	(**S**)
	i, i+4 orientation			**di-Cps**				
	di-Cps		E4	-Phe-Ala-Ala-**Cps**-**Cps**-			***Cps-Pps***	
B2	-**Cps**-Ala-Ala-Aib-**Cps**-	(**S**)	E5	-**Cps**-**Cps**-Ala-Ala-Phe-		H4	-Phe-Ala-**Cps**-**Pps**-	
B3	-**Cps**-Ala-Ala-Phe-**Cps**-	(**S**)	E6	-Val-Ala-Ala-**Cps**-**Cps**-		H5	-Val-Ala-**Cps**-**Pps**-	
B4	-**Cps**-Phe-Ala-Aib-**Cps**-		E7	-**Cps**-**Cps**-Ala-Ala-Val-		H6	-His-Ala-**Cps**-**Pps**-	
B5	-**Cps**-Ala-Ala-Val-**Cps**-		E8	-His-Ala-Ala-**Cps**-**Cps**-		H7	-Ile-Ala-**Cps**-**Pps**-	
B6	-**Cps**-Val-Ala-Aib-**Cps**-		F1	-**Cps**-**Cps**-Ala-Ala-His-				
B7	-**Cps**-Ala-Ala-His-**Cps**-		F2	-Ile-Ala-Ala-**Cps**-**Cps**-				
B8	-**Cps**-His-Ala-Aib-**Cps**-		F3	-**Cps**-**Cps**-Ala-Ala-Ile-				
C1	-**Cps**-Ala-Ala-Ile-**Cps**-	(**S**)						
C2	-**Cps**-Ile-Ala-Aib-**Cps**-			***i, i+1 orientation***				
				Cps-Pps				
	i, i+4 orientation		F4	-Phe-Ala-Ala-**Pps**-**Cps**-				
	Cps-Pps		F5	-**Cps**-**Pps**-Ala-Ala-Phe-				
C3	-**Cps**-Ala-Ala-Aib-**Pps**-		F6	-Val-Ala-Ala-**Pps**-**Cps**-				
C4	-**Cps**-Ala-Ala-Phe-**Pps**-	(**S**)	F7	-**Cps**-**Pps**-Ala-Ala-Val-				
C5	-**Cps**-Phe-Ala-Aib-**Pps**-		F8	-His-Ala-Ala-**Pps**-**Cps**-				
C6	-**Cps**-Ala-Ala-Val-**Pps**-	(**S**)	G1	-**Cps**-**Pps**-Ala-Ala-His-				
C7	-**Cps**-Val-Ala-Aib-**Pps**-	(**R**)	G2	-Ile-Ala-Ala-**Pps**-**Cps**-				
C8	-**Cps**-Ala-Ala-His-**Pps**-		G3	-**Cps**-**Pps**-Ala-Ala-Ile-				
D1	-**Cps**-His-Ala-Aib-**Pps**-	(**R**)						
D2	-**Cps**-Ala-Ala-Ile-**Pps**-	(**S**)						
D3	-**Cps**-Ile-Ala-Aib-**Pps**-							

The first library synthesized contained 63 members. The peptides in this library were a mixture of types. The first 27 peptides had the phosphine containing amino acids in an i, i+4 relationship. This was done with the assumption that even on the solid support the peptides would adopt the helical structure necessary for metal coordination. Three amino acids (Ala-Aib-Ala) were placed on each end of the peptide. These residues were

conserved through out the library. Nine peptides (**A1-B1**) with two Pps residues were synthesized along with nine (**B2-C2**) containing two Cps residues and nine (**C3-D3**) with Cps and Pps. The remaining 36 peptides (**D4-H7**) had the phosphine amino acids positioned next to each other.

Table 1 Screening of Library



	1	2	3	4	5	6	7	8
A	S 5.3 (24.0)	R 7.6 (17.4)	S 1.7 (7.3)	R 7.8 (26.2)	R 6.9 (18.1)	R 4.8 (2.4)	R 17.0 (1.4)	R 5.9 (11.3)
B	S 2.4 (38.0)	S 18.3 (6.4)	S 15.7 (3.4)	S 2.9 (16.3)	S 1.0 (2.8)	S 5.8 (8.0)	S 8.2 (3.9)	S 3.4 (28.8)
C	S 11.6 (6.2)	S 2.0 (38.2)	S 5.2 (62.7)	S 11.9 (12.8)	S 4.9 (21.9)	S 12.7 (60.0)	R 10.2 (58.1)	R 6.6 (97.4)
D	R 11.8 (100)	S 17.4 (2.3)	0.0 (36.3)	S 2.6 (8.5)	R 2.0 (15.9)	S 1.8 (11.4)	S 4.9 (12.1)	R 4.5 (25.1)
E	S 6.7 (35.7)	S 11.4 (9.5)	0.0 (1.7)	S 6.7 (29.5)	R 4.6 (32.0)	R 5.7 (72.8)	S 5.8 (19.3)	R 3.7 (100)
F	0.0 (100)	S 0.8 (52.7)	0.0 (1.0)	S 4.4 (18.8)	R 9.3 (54.5)	0.0 (1.0)	0.0 (3.4)	R 10.3 (89.5)
G	S 1.0 (52.8)	S 5.8 (40.0)	0.0 (36.3)	S 1.4 (28.4)	S 7.4 (15.8)	0.0 (61.2)	S 3.4 (38.3)	S 5.1 (9.5)
H	R 5.0 (13.2)	0.0 (43.7)	S 11.7 (8.0)	R 3.0 (21.6)	S 1.6 (19.0)	R 8.0 (2.2)	S 6.1 (17.6)	

Top number % ee of (R) or (S) enantiomer. Bottom number % conversation.

Peptides **A1-B1** were then varied in following manner. **A1** was the parent in the 9 member series. **A2** has Phe in the i+3 position followed by **A3** with Phe in the i+1 position. Peptides **A4** and **A5** have Val in the same orientation as Phe in the previous two. **A6** and **A7** contain His in the same manner followed by **A8** and **B1** with Ile positioned in the same way. This pattern was then repeated in the di Cps (**B2-C2**) and Cps-Pps (**C3-D3**) peptides. The odd residues (Phe, Val, His, Ile) were all placed in such a manner as to potentially be positioned near the metal in a helical peptide. The remaining 36 peptides with the phosphine amino acids positioned next to each other have the amino acids Phe, Val, His and Ile placed in positions where they may be near the metal, depending on the conformation of the metal complex.

As the first reaction to screen we chose the hydrogenation of methyl 2-acetamidoacrylate.[25-27] The major concern with a combinatorial approach is that all the members of a library will give consistently poor results and no correlation will be identified. Fortunately, this was not the case. In figure 2 an **S** or an **R** has been placed next to ligands that give either the **S** or the **R** enantiomer in greater than 10% ee. The noticeable trend is that all the ees of greater than 10% of the **S** enantiomer are with peptides that contain at least one dicyclohexylphosphinoserine (Cps). Within that group is a second trend. That trend is that the peptides that gave the best results all have the unique amino acid in the i+3 position (**B2, B3, C1, C4, C6,** and **D2**). Another more tenuous correlation may exist with all the **R** enantiomers in greater than 10% occurring when the unique amino acid was in the i+1 position (**A7, C7,** and **D1**). Whether this last correlation is significant has yet to be

determined.

The hydrogenations were run in a Parr high pressure reactor at room temperature in THF solvent. Each pin with the peptide phosphine rhodium complex attached was placed in a scintillation vial. Twenty-four vials were loaded in a Parr bomb (400 psi) and the entire assembly was then agitated on an orbital shaker. To increase through put the reactions were run to only 10 to 40% completion. We have determined that longer reaction times can be used to obtain complete reaction. The selectivity of the reactions was screened by injection of the each crude reaction mixture on to a GC equipped with a chiral capillary column (Chiraldex B-TA 10 m x 0.25 mm).

While the enantiomeric excesses obtained for our first library were moderate we were gratified to find that the method is a viable approach to the synthesis and testing of new chiral phosphine ligands. That there appears to be some correlation between peptide sequence and selectivity is further gratifying. We are currently approaching the development of ligands in two ways. We are in the process of synthesizing a number of the more promising ligands on a larger scale to characterize their structure and to evaluate their ability to catalyze the reaction in a homogenous system. We are also in the process of synthesizing a second library where the amino acids in the i+3 position have larger side chains. Along with these approaches we are also screening a variety of other substitution patterns.

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