

The Parallel Synthesis of Peptide Based Phosphine Ligands

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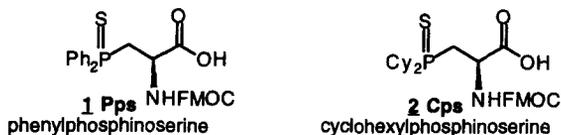
Abstract: Chemistry is reported that allows for the synthesis and screening of phosphine ligands by standard combinatorial technology. To demonstrate the method, libraries of phosphine containing peptides were synthesized. Rhodium was complexed to the phosphine ligands while they were attached to the synthesis support. Each member of the library was screened for its ability to catalyze the asymmetric hydrogenation of enamides. © 1999 Elsevier Science Ltd. All rights reserved.

Over the last few years we have been involved in the development of chemistry that allows the incorporation of phosphine groups into peptide structures.¹⁻⁵ At its core, this project has two goals. First, through the incorporation of transition metals into stable three-dimensional structures it may be possible to develop catalysts that have unique selectivity. Second, with the appropriate build blocks in hand it should be possible to use combinatorial, or parallel synthetic, methods to synthesize libraries of phosphine transition metal complexes. Secondary to the primary goals, one should be able to synthesize catalysts that can be used while bound to polymer supports, as well as catalysts that may work in a wide variety of solvents. This paper reports the synthesis of phosphine containing peptide libraries that have the metal coordinating phosphine groups positioned in three different orientations. These libraries are evaluated for their ability to catalyze asymmetric hydrogenation while the complex is attached to a polymer support as well as in a number of solvents, including water.

A number of approaches have been taken in the use of combinatorial chemistry for the development of new selective ligands. Ellman has synthesized a library of amino alcohols for use as ligands in controlling the addition of diethylzinc to aromatic aldehydes.⁶ Hoveyda and Snapper have synthesized libraries of hydroxy imines and shown them to be useful in the selective opening of meso epoxides.^{7,8} Most recently, Jacobsen used parallel methods in the discovery of a Schiff-base catalyst for the asymmetric Strecker reaction.⁹ These approaches focus on Lewis acid catalyzed reactions with the ligands being nitrogen and oxygen. The system reported here is complementary to these systems since the types of catalytic metals the phosphine system is being developed for are rhodium, platinum and palladium. These catalysts have potential in the catalysis of a different set of reactions from those catalyzed by more Lewis acidic metals.

Building Blocks

In previous papers, we have reported the synthesis of phosphine-containing serine derivatives **1** and **2**.^{1,2} We have shown these molecules are effective building blocks for the synthesis of phosphorus-containing

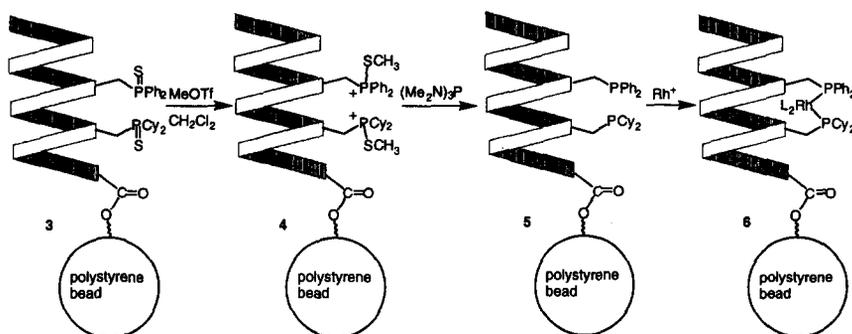


peptides. Chemistry has been developed that allows for the conversion of the phosphine sulfide group into a phosphine and the subsequent metalation with rhodium. Once the chemistry was developed for these steps, we were ready to build libraries of ligands.

There are a wide variety of combinatorial methods available for this task. In selecting which method of parallel synthesis to use, the driving force often has little to do with the type of synthetic chemistry used to assemble the library. The most important issue is often which method is compatible with the screen that is going to be used to evaluate the library. When screening members of a library containing ligands for asymmetric catalysis, the screen is ultimately selectivity of catalysis. In general, such a screen precludes the use of synthetic methods that give mixtures of compounds, such as split and pool methods. For this reason, the spatially addressable Chiron Multipin™ Multiple Peptide Synthesis system was chosen, allowing the synthesis of discrete isolated compounds.¹⁰⁻¹⁵ The parallel synthesis of peptides on crowns in a 96-pin format gives the spatially addressable libraries we require, with a minimum of optimization necessary. In this system the identity of each peptide ligand attached to a given crown is known, and screening of individual ligand metal complexes can 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 attached to the macrocrown support. For this to be possible, it was necessary for us to develop a method of desulfurization that was compatible with the ligands remaining attached to the solid support. In our original work we used Raney nickel to remove the sulfur from the phosphorus.^{1,2} This chemistry was clearly not compatible with running one hundred or more reactions simultaneously or with removal of the sulfur while the ligand remained attached to the support. The homogenous method we ultimately developed is based on the report by Omelanczuk and Mikolajczyk that after alkylation of the phosphorus sulfide the sulfur can be transferred to the phosphorus of HMPT (Scheme 1).^{5,16} This type of reaction is ideally suited for solid phase chemistry, since a large excess of HMPT can be used to drive the reaction to completion without causing difficulty in the isolation of the product.

Scheme 1; Removal of Sulfur From Peptides Attached to Support



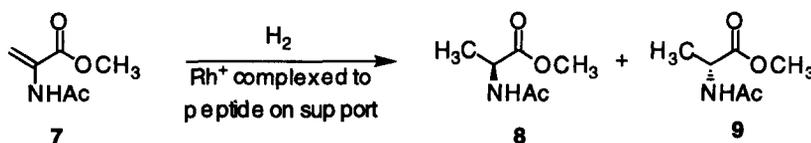
The hydrogenation of methyl 2-acetamidoacrylate was chosen as the first reaction to screen (Scheme 2)¹⁷⁻¹⁹ This reaction was chosen to demonstrate the potential of this type of system to find catalysts with varying degrees of selectivity, and not because we felt we could find a ligand that performs this reaction with greater selectivity than DuPHOS, which gives greater than 99% ee for this type of substrate. A 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 1 an **S** or an **R** has been placed next to ligands that gave either the **S** or the **R** enantiomer in greater than 10% ee. A noticeable trend is that all the peptides that gave ees of greater than 10% of the **S** enantiomer contain at least one dicyclohexylphosphoserine (Cps). Within that group the peptides that gave the best results all have the unique amino acid (Aib, Phe, Val, Ile) in the $i + 3$ position (**B1**, **B2**, **B8**, **C2**, **C4**, and **C8**). 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**, **C5**, and **C7**). Whether this last correlation is significant has yet to be determined. While these selectivities are considerably lower than the best systems known for this reaction, it does demonstrate the feasibility of this approach.

Table 1 Hydrogenation of methyl 2-acetamidoacrylate

	1	2	3	4	5	6	7	8	9
A	5.3 s (24.0)	7.6 r (17.4)	1.7 s (7.3)	7.8 r (26.2)	6.9 r (18.1)	4.8 r (2.4)	17.0 r (1.4)	5.9 r (11.3)	2.4 s (38.0)
B	18.3 s (6.4)	15.7 s (3.4)	2.9 s (16.3)	1.0 s (2.8)	5.8 s (8.0)	8.2 s (3.9)	3.4 s (28.8)	11.6 s (6.2)	2.0 s (38.2)
C	5.2 s (62.7)	11.9 s (12.8)	4.9 s (21.9)	12.7 s (60.0)	10.2 r (58.1)	6.6 r (97.4)	11.8 r (100)	17.4 s (2.3)	0.0 (36.3)
D	2.6 s (8.5)	2.0 r (15.9)	1.8 s (11.4)	4.9 s (12.1)	4.5 r (25.1)	6.7 s (35.7)	11.4 s (9.5)	0.0 (1.7)	6.7 s (29.5)
E	4.6 r (32.0)	5.7 r (72.8)	5.8 s (19.3)	3.7 r (100)	0.0 (100)	0.8 s (52.7)	0.0 (1.0)	4.4 s (18.8)	9.3 r (54.5)
F	0.0 (1.0)	0.0 (3.4)	10.3 r (89.5)	1.0 s (52.8)	5.8 s (40.0)	0.0 (36.3)	1.4 s (28.4)	7.4 s (15.8)	0.0 (61.2)
G	3.4 s (38.3)	5.1 s (9.5)	5.0 r (13.2)	0.0 (43.7)	11.7 s (8.0)	3.0 r (21.6)	1.6 s (19.0)	8.0 r (2.2)	6.1 s (17.6)

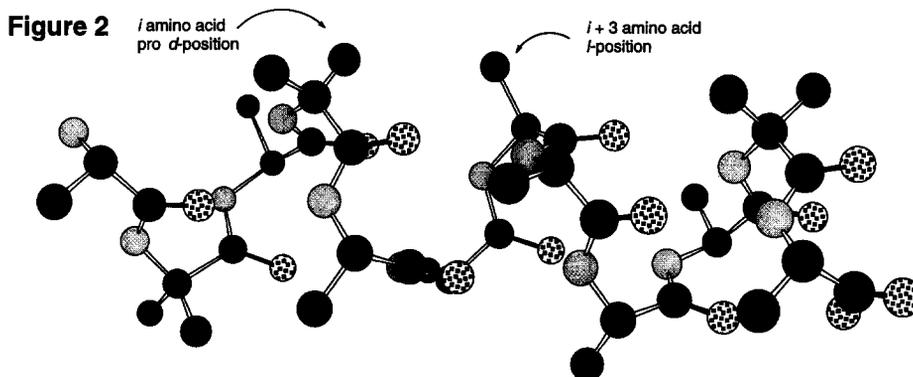
a.) Numbers followed by letter s or r are enantiomeric excess in favor of s or r enantiomer. b.) Enantiomeric excesses are reported to $\pm 0.5\%$ as determined by chiral capillary GC. c.) Numbers in parentheses are percentage conversions. d.) The reactions were run at room temperature with 300 psi hydrogen pressure.

Scheme 2 Hydrogenation of methyl 2-acetamidoacrylate



Second Generation Library

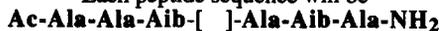
While the ability to make a large number of compounds is potentially a powerful tool for the discovery of new catalysts, logic and chemical principals are also necessary when deciding what libraries to synthesize. Given the moderate results obtained with the library in which the phosphines were positioned i , $i + 4$ to each other, we decided to examine other possible orientations for the phosphine containing amino acids. Analysis of models of α -helical peptides indicates that there are phosphine positions other than i , $i + 4$ that are potentially useful. Modeling indicates that the side chain of a d -amino acid in the i position of an α -helix is in close proximity to the side chain of an l -amino acid in the $i + 3$ position. Figure 2 illustrates that these two groups point toward each other. With this in mind we chose to synthesize a library containing peptides with the phosphine side chains in this orientation. This library consists of twenty four peptides, each twelve residues in length, with a d -phosphine-containing amino acid in the i position and a l -phosphine-containing amino acid in the $i + 3$ position. Twelve of the peptides contain phenylphosphinoserine in both positions while twelve others have cyclohexylphosphinoserine as the $i + 3$ amino acid. In each grouping of twelve, there are six peptides with Ala, Asp, His, Phe, Trp, and Val in the position before the i positioned phosphine and six with those amino acids in the $i + 4$ position. The other 24 peptides in the library consist of thirteen residue peptides with d -phenylphosphinoserine in the i position and either l -phenylphosphinoserine or l -cyclohexylphosphinoserine in the $i + 4$ position. Within those groups of peptides the amino acids Ala, Asp, His, Phe, Trp, and Val are placed in either the $i + 1$ or $i + 3$ locations.



The data for each catalyst in the hydrogenation of methyl 2-acetamidoacrylate are presented in Table 2. The hydrogenations were run in a Parr high pressure reactor at room temperature in THF. 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 throughput, 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 for the reactions was determined by GC analysis of the crude reaction mixture, using a chiral capillary column (Chiraldex B-TA 10 m x 0.25 mm).

Figure 3 Sequences synthesized by combinatorial approach

Each peptide sequence will be



A1 Ala-dPps-Ala-Ala-Pps-Ala	D1 Ala-dPps-Ala-Ala-Cps-Ala	G1 Ala-dPps-Ala-Ala-Ala-Pps-Ala
A2 Asp-dPps-Ala-Ala-Pps-Ala (S)	D2 Ala-dPps-Ala-Ala-Cps-Asp	G2 Ala-dPps-Ala-Ala-Asp-Pps-Ala
A3 His-dPps-Ala-Ala-Pps-Ala	D3 Ala-dPps-Ala-Ala-Cps-His	G3 Ala-dPps-Ala-Ala-His-Pps-Ala
A4 Phe-dPps-Ala-Ala-Pps-Ala	D4 Ala-dPps-Ala-Ala-Cps-Phe	G4 Ala-dPps-Ala-Ala-Fhe-Pps-Ala
A5 Trp-dPps-Ala-Ala-Pps-Ala (S)	D5 Ala-dPps-Ala-Ala-Cps-Trp	G5 Ala-dPps-Ala-Ala-Trp-Pps-Ala
A6 Val-dPps-Ala-Ala-Pps-Ala	D6 Ala-dPps-Ala-Ala-Cps-Val	G6 Ala-dPps-Ala-Ala-Val-Pps-Ala
B1 Ala-dPps-Ala-Ala-Cps-Ala	E1 Ala-dPps-Ala-Ala-Ala-Pps-Ala	H1 Ala-dPps-Ala-Ala-Ala-Cps-Ala
B2 Asp-dPps-Ala-Ala-Cps-Ala	E2 Ala-dPps-Asp-Ala-Ala-Pps-Ala (S)	H2 Ala-dPps-Ala-Ala-Asp-Cps-Ala
B3 His-dPps-Ala-Ala-Cps-Ala	E3 Ala-dPps-His-Ala-Ala-Pps-Ala	H3 Ala-dPps-Ala-Ala-His-Cps-Ala
B4 Phe-dPps-Ala-Ala-Cps-Ala	E4 Ala-dPps-Phe-Ala-Ala-Pps-Ala	H4 Ala-dPps-Ala-Ala-Fhe-Cps-Ala
B5 Trp-dPps-Ala-Ala-Cps-Ala	E5 Ala-dPps-Trp-Ala-Ala-Pps-Ala	H5 Ala-dPps-Ala-Ala-Trp-Cps-Ala
B6 Val-dPps-Ala-Ala-Cps-Ala (S)	E6 Ala-dPps-Val-Ala-Ala-Pps-Ala (S)	H6 Ala-dPps-Ala-Ala-Val-Cps-Ala
C1 Ala-dPps-Ala-Ala-Pps-Ala (S)	F1 Ala-dPps-Ala-Ala-Ala-Cps-Ala	
C2 Ala-dPps-Ala-Ala-Pps-Asp	F2 Ala-dPps-Asp-Ala-Ala-Cps-Ala	
C3 Ala-dPps-Ala-Ala-Pps-His	F3 Ala-dPps-His-Ala-Ala-Cps-Ala	
C4 Ala-dPps-Ala-Ala-Pps-Phe	F4 Ala-dPps-Phe-Ala-Ala-Cps-Ala	
C5 Ala-dPps-Ala-Ala-Pps-Trp (S)	F5 Ala-dPps-Trp-Ala-Ala-Cps-Ala	
C6 Ala-dPps-Ala-Ala-Pps-Val (S)	F6 Ala-dPps-Val-Ala-Ala-Cps-Ala	

Table 2 Hydrogenation of methyl 2-acetamidoacrylate

	1	2	3	4	5	6
A	20.2 s (4.8)	37.7 s (2.2)	15.4 s (1.1)	14.4 s (1.1)	36.0 s (1.4)	0.0 (38.0)
B	10.3 s (3.1)	14.5 s (1.8)	3.6 s (2.7)	0.0 (4.4)	14.3 s (8.4)	32.2 s (4.5)
C	22.0 s (8.0)	10.4 s (6.3)	17.7 s (5.5)	13.4 s (5.6)	29.9 s (8.2)	19.9 s (4.4)
D	0.0 (7.0)	13.8 s (2.8)	6.3 s (3.9)	3.4 r (9.3)	3.4 r (15.9)	0.0 (3.6)
E	4.1 s (27.3)	20.1 s (33.9)	9.0 s (5.2)	6.0 s (34.7)	4.1 s (58.0)	24.4 s (45.4)
F	14.0 s (8.3)	9.6 s (12.2)	6.8 s (12.7)	7.0 s (20.5)	8.0 s (24.0)	5.6 s (22.7)
G	18.6 s (53.5)	13.2 s (25.6)	16.0 s (4.2)	10.6 s (31.6)	11.8 s (43.2)	8.4 s (25.1)
H	9.4 s (24.5)	13.8 s (12.6)	6.6 s (3.2)	0.0 (15.6)	6.0 s (18.7)	1.6 s (27.7)

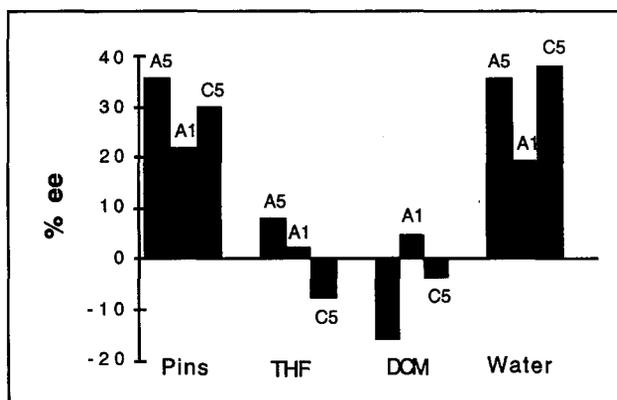
a.) Numbers followed by letter s or r are enantiomeric excess in favor of s or r enantiomer. b.) Enantiomeric excesses are reported to $\pm .5\%$ as determined by chiral capillary GC. c.) Numbers in parentheses are percentage conversions. d.) The reactions were run at room temperature with 300 psi hydrogen pressure.

In general the selectivity for this set of reactions was higher than our original library. The peptides possessing the unique amino acid at the position just before the *d*-amino acid gave the highest selectivity.

Peptide **A2** with aspartate in that position gave the highest selectivity (38% ee) and peptide **A5** with tryptophan gave nearly the same preference.

Homogenous Catalysis

To determine if the results obtained with the catalysts while they are attached to a solid support correlate to selectivities obtained with these catalysts in solution, three of the most selective peptides were synthesized on polystyrene resin, cleaved from the support and their selectivities checked in a number of solvents. Peptides **A1**, **A5** and **C5** were synthesized by standard peptide methods on polystyrene using a Rink handle. The hydrogenation reactions were performed, using THF, CH₂Cl₂ and water respectively as solvents. The results are shown in Figure 4. The original catalysis with the catalysts bound to the support were run in THF solvent. The catalysis with the soluble peptides in THF gave results that not only did not correlate with the results on the pins but actually yielded the opposite enantiomer as the major product with peptide **C5**. A similar result was observed when the reactions were run in dichloromethane, with two peptides giving the R enantiomer as the major product. The origin of this effect is not yet clear and is still being investigated. It is very interesting that the solvent that gives the highest selectivity and most closely mirrors the results on pins is water. The peptides studied are highly hydrophobic and not particularly soluble in water. It is quite likely that these peptides are aggregated in water and may actually have some sort of tertiary structure. It is also tempting to suggest that these aggregates are similar to the structures formed when the peptides are attached to the solid support. We are in the process of studying resins with different loadings to determine if the local concentration on the resin has an effect on the selectivity of these catalysts. We are also designing catalysts that will form helix bundles in solution to determine if this is another element of control we may be able to take advantage of.



Enantiomeric excesses are reported to $\pm 0.5\%$ as determined by chiral capillary GC.

- (A5) Ac-Ala-Ala-Aib-Trp-dPps-Ala-Ala-Pps-Ala-Ala-Aib-Ala-NH₂
 (A1) Ac-Ala-Ala-Aib-Ala-dPps-Ala-Ala-Pps-Ala-Ala-Aib-Ala-NH₂
 (C5) Ac-Ala-Ala-Aib-Ala-dPps-Ala-Ala-Pps-Trp-Ala-Aib-Ala-NH₂

Figure 4 Solvent effects on hydrogenation of methyl 2-acetomidoacrylate

Conclusion

While the enantiomeric excesses obtained for the first two libraries were moderate, it is satisfying to find that the method is a viable approach to the synthesis and testing of new chiral phosphine ligands. These two libraries represent the first example of a combinatorial phosphine ligand system. It is further gratifying that there appears to be some correlation between peptide sequence and selectivity. It seems quite clear that the stereochemical outcome of the catalytic hydrogenation can be influenced by placing unique residues at key positions. We are currently synthesizing libraries of peptide based phosphine ligands that take advantage of secondary structures other than helices.

Experimental

The Multipin combinatorial system with Fmoc-Gly-HMD-MA/DMA crowns (6.2 μmol capacity) was obtained from Chiron Mimetopes, Ltd., Australia. Methyl 2-acetamidoacrylate and $[\text{Rh}(\text{NBD})\text{Cl}]_2$ were purchased from Aldrich Chemicals, Inc and were used without further purification unless otherwise noted. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories and used without further purification.

Capillary GC data were obtained using a Shimadzu Model GC-14A instrument equipped with a FID detector, a Shimadzu CR601 integrator and a 10 m \times 0.25 mm ChiralDEX B-TA column.

The hydrogenation reactions were run in a Parr high pressure reactor at room temperature in THF. Each crown with the peptide-phosphine rhodium complex was placed in a scintillation vial. Twenty-four vials were loaded in a Parr bomb (500 psi) and the entire assembly was then agitated on an orbital shaker.

General procedure for preparation of the catalysts and hydrogenation

Peptides were synthesized on the crowns with 6.2 μmol capacity by Fmoc strategy, using DIC/HOBt activation. To insure that the peptide couplings were proceeding as assumed, the identity of members of the library in Figure 1 was checked by Matrix-Assisted Laser Desorption mass spectrometry (MALDI-MS). Initially peptides to be screened were left on the crowns, which were then disconnected from the stems, transferred to individual vials and sealed under nitrogen with rubber septa. Each crown was then treated with $\text{CF}_3\text{SO}_3\text{CH}_3$ (3.5 μL , 31.0 μmol) in CH_2Cl_2 (2.5 mL) for 6 hours. Following methylation the crowns were then washed with CH_2Cl_2 (3 \times 3 mL) and THF (3 \times 3 mL) respectively. The crowns were treated with HMPT (85%, 8.0 μL , 37.2 μmol) in THF (2 mL) for 2 hours. After washing with THF (3 \times 3 mL) and methanol (3 \times 3 mL), the crowns were metalated by treatment with a solution of $\text{Rh}(\text{NBD})\text{Cl}^+ \text{ClO}_4^-$ in methanol for 15 minutes (prepared by stirring $[\text{Rh}(\text{NBD})\text{Cl}]_2$ (1.5 mg, 3.2 μmol) and AgClO_4 (1.3 mg, 6.4 μmol) in methanol (2.5 mL) for 15 minutes and filtering off the AgCl precipitate). Upon addition of the rhodium the crowns turned a yellow color. After treatment with rhodium the crowns were washed with methanol.

The crowns with peptide metal complexes attached were then placed in vials to which methyl 2-acetamidoacrylate **7** (10 mg, 70 μmol) in THF (2.0 mL) were added. The vials were then placed in a Parr pressure reactor, which was purged with nitrogen. After the nitrogen purge the bomb was charged with

hydrogen to 500 psi (Figure 5). The pressure reactor was then placed on an orbital shaker and the vials were agitated for 48 hours. After the allotted time, the reactions were analyzed by injection of each crude hydrogenation reaction mixture on to a GC equipped with a chiral capillary column (Chiraldex B-TA 10 m × 0.25 mm).

Figure 5 Screening of catalytic hydrogenation

The pins were disconnected from stems and transferred to individual vials. Each pin has a single peptide attached.

The vials were then sealed under nitrogen.

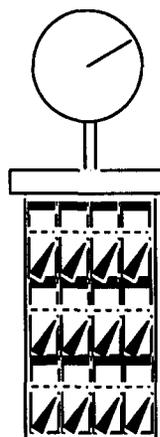
The pins were treated with methyl triflate, HMPT and Rh(I) subsequently *via* syringe with thorough washing after each treatment.



The pins turned a yellow color upon the final treatment.

The seals were punctured with a needle and then stacked in an autoclave.

The autoclave was pressurized with H₂ or H₂/CO, and catalysis performed.



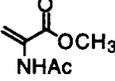
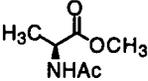
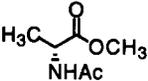
As a control, a peptide without phosphine containing amino acids was synthesized [Ac-Ala-Aib-Ala-Ala-Ala-Ala-Aib-Ala-Ala-Ala-Ala-Aib-Ala-polymer]. This peptide was treated with [Rh(NBD)⁺ - ClO₄⁻] by exactly the same procedure as peptide as the libraries in Figure 1 and 3. This peptide did not take up the yellow color characteristic of a rhodium complex and did not catalyze the hydrogenation of enamide **7**. This is evidence that the catalysis observed with the peptides in Figures 1 and 3 is due to the phosphine metal complex and not free rhodium or rhodium complexed to other groups on the peptide.

A general procedure for study of solvent effects

The peptide sequences of interest were synthesized on Rink resin by standard Fmoc protocol,²⁰ and cleaved from the resin by treatment with 2% TFA in 1,2 dichloroethane. The peptides were used directly without further purification. The purity the peptides was found to be between 90 and 95% based on HPLC analysis. A sample of each peptide (13.0 μmol) was dissolved in degassed methanol (3.0 mL) in a Schlenk tube. Raney nickel slush (300 mg) was washed with methanol, and was then added to the tube under nitrogen. The reaction mixture was stirred at room temperature for 8.0 hours, by which time ³¹P NMR spectrum indicated complete conversion of the phosphine sulfide to the phosphine. Raney nickel was then filtered through Celite under nitrogen and the filtrate was concentrated under vacuum to 0.5 ml. [Rh(NBD)Cl]₂ (1.5 mg, 3.2 μmol) and AgClO₄ (1.3 mg, 6.4 μmol) were mixed under nitrogen in 0.1 mL of methanol and stirred at room temperature

for 20 minutes. The solution was filtered through Celite and the filtrate was introduced to the above dodecamer solution which immediately turned golden yellow upon addition. The rhodium complex solution was then concentrated to 0.3 mL, 0.1 mL of which was added to each of the three vials which contained a solution of methyl 2-acetamidoacrylate (20.0 mg, 130 μ mol) in THF (2.0 mL), CH_2Cl_2 (2.0 mL) and water (2.0 mL) respectively. The vials were capped with a punctured plastic cap and put in a Parr autoclave. The autoclave was purged with nitrogen and was filled with H_2 to 300 psi. The autoclave was then put on an orbital shaker and was shaken for 60 hours. At the end of this period, the bomb was vented and opened. The reaction mixture was directly analyzed by GC without purification.

Table 3 Retention times of starting material and products on Chiraldex B-TA 10 m x 0.25 mm

 4-1	 4-2	 4-3
8.26	12.62	14.46

GC Conditions: 80 °C isothermal; Injection
Temp., 200 °C; Detection Temp., 200 °C

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