Asymmetric Catalysis with Libraries of Palladium β-Turn Phosphine Complexes

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Given their ability to assume stable secondary structures, small peptides are beginning to be used as scaffolds for a variety of applications in chemistry. Imperiali has used peptides to organize ligands for metals as specific ion sensors.[1] Miller has used the β-turn structural motif in the design of catalysts for selective acylations.[2,3] Besides providing unique platforms for the arrangement of atoms in space, peptides offer the opportunity to build a large number of derivatives of a given molecule type. This can easily be done by a wide variety of methods that allow for the synthesis of libraries of peptides.[4−6] A third feature of solid-phase peptide synthesis is that it provides the desired molecules immobilized on a solid support. It has been with these three aspects in mind that we have developed a system that allows for the incorporation of amino acids possessing protected phosphine groups into nearly any peptide structure synthetically accessible.[7−12] Such a system allows for the synthesis of large numbers of new catalysts that have predictable structures, that ideally will perform selective catalysis while attached to an insoluble polymer. This paper reports the synthesis of phosphine libraries based on the well-known β-turn forming motif -Pro-D-Yyy-, where Yyy is a D-amino acid.[1,13,14] These libraries were then used to bind palladium and catalyze the addition of malonate to cyclopentenyl acetate.[1,14]

The basic ligand design consists of the turn-forming sequence Pro-D-Yyy with the metal-binding phosphine-containing amino acids flanking this element. Examination of the basic structure indicated that a β-turn secondary structure would allow for coordination of a transition metal into this asymmetric environment. Before the first library was produced a sample peptide was synthesized to determine if this structure was viable as a metal ligand as well as to determine if such a complex would be catalytically active. The initial complex that was synthesized and tested was Ac-Pps-Pro-D-Ala-Pps-Gly resin. Pps represents (diphenylphosphino)serine, a phosphine-containing amino acid we have developed previously.[7,8,10,11] The phosphine sulfide-containing peptide was synthesized by solid-phase peptide synthesis followed by conversion to the free phosphine (Scheme 1).[11] We were quite gratified that this initial ligand behaved as expected in terms of synthesis and deprotection of the phosphines.

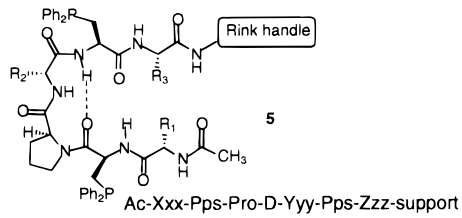
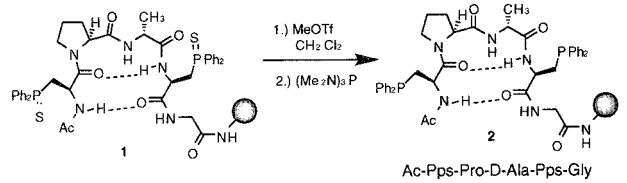


Figure 1.

Scheme 1



Scheme 2

Coordination of palladium gave a metal complex that catalyzed the addition of dimethyl malonate to cyclopentenyl acetate in 60% ee (Scheme 2). This was while the complex was attached to the polymer support used in its synthesis. We felt this was an excellent starting point given that there are few catalyst systems that catalyze this reaction in high ee.[15−21]

With this positive initial result in hand we designed the first library to be synthesized. The ligands were synthesized on I-series MD-SynPhase Crowns from Chiron Technologies. Our original design was to attempt to screen the libraries of ligands while they were attached to the solid support. The structural features that were varied in this initial library were adding and then varying amino acids at the N-terminus, the substitution of amino acids other than Gly at the C-terminal end of the peptide, and substitutions of D-amino acids other than D-Ala next to the proline. The basic sequence examined in the library was Ac-Xxx-Pps-Pro-D-Yyy-Pps-Zzz-Rink (Figure 1). Amino acids placed in the Xxx and Zzz locations were Ala, Gly, Phe, Glu, Cys, Ser, Lys, Tyr, D-Ala, D-Met, D-Phg, D-Val, D-Phe as well as Phg, His, and Trp at the Xxx position only. The amino acids placed at the critical turn-forming position Yyy were D-Ala, D-Phe, D-Val, D-Leu, D-Met, D-Phg, and Gly. These amino acids were combined to form a 96-member library. The members of this library were tested for their ability to catalyze the asymmetric addition of dimethyl malonate to cyclopentenyl acetate. The selectivities obtained with this library ranged from 34% ee for the lowest to 80% ee in the case of the highest selectivity.[22] There were 77 members of the library that gave 60% or greater selectivity. In the Zzz position,

(1) Imperiali, B.; Kapoor, T. M. *Tetrahedron* **1993**, *49*, 3501−3510.
(2) Copeland, G. T.; Jarvao, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.
(3) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
(4) Pirrung, M. C. *Chem. Rev.* **1997**, *97*, 473−488.
(5) DeWitt, S. H.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114−122.
(6) Bray, A. M.; Jhingran, A. G.; Valerio, R. M.; Maeji, N. J. *J. Org. Chem.* **1994**, *59*, 2197−2203.
(7) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481−4482.
(8) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434−435.
(9) Gilbertson, S. R.; Pawlick, R. V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 902.
(10) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475−6478.
(11) Gilbertson, S. R.; Wang, X.; Hoge, G. S.; Klug, C. A.; Schaefer, J. *Organometallics* **1996**, *15*, 4678−4680.
(12) Gilbertson, S. R.; Chen, G.; Kao, J.; Beatty, A.; Campana, C. F. *J. Org. Chem.* **1997**, *62*, 5557−5566.
(13) Imperiali, B.; Fisher, S. L. *J. Org. Chem.* **1992**, *57*, 757.
(14) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182−3188.
(15) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235−236.
(16) Trost, B. M.; Bunt, R. C. *Angew. Chem, Int. Ed. Engl.* **1996**, *35*, 99−102.
(17) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662−9670.
(18) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
(19) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3047−3050.
(20) Knühl, G.; Sennhenn, P.; Helmchen, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1845−1846.
(21) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513−518.
(22) For a complete listing of the libraries synthesized and the selectivities obtained with these libraries see the Supporting Information.

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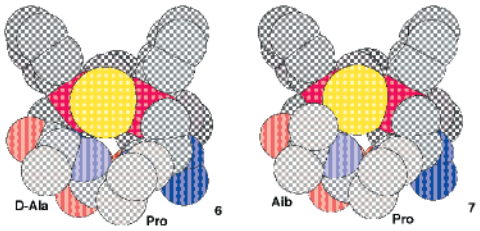


Figure 2.

with the exception of sulfur-containing amino acids, residues with larger side chains seem to give higher selectivity. In the Xxx position higher selectivities were obtained with D-Ala, Ala, and Gly, amino acids with smaller side chains. Some of the highest selectivities were obtained when D-amino acids were place in positions Xxx and Zzz. The best ligand (D-Phg-Pps-Pro-D-Val-Pps-D-Leu-) has been synthesized and tested on 20 separate occasions, it consistently gives selectivity of 75% ee ± 2%.[23] To test if any of the residues were undergoing racemization, these peptides were synthesized by a wide variety of methods. Additionally this peptide was purified and tested in solution.

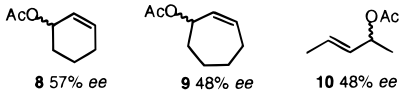
Figure 2 is a space-filled representation of our working model for these ligands. Examination of secondary structure by NMR indicates the molecule has the expected β-turn secondary structure. NOESY data for the initial parent sequence **6** (Ac-Pps-Pro-D-Ala-Pps-Gly-NH_2) is consistent with a turn structure, with dipolar exchange observed between the CH_2 groups next to each of the phosphine sulfides. Additionally dipolar exchange was observed between the D-Ala N−H and the H of proline. IR data was consistent with the H of the $i + 3$ NH being internally hydrogen bonded to the amide carbonyl of the i residue.

If our view of the structure of the active palladium complex is correct, one would expect substitutions of amino acids Xxx and Zzz to have a small effect on the selectivity of the catalyst. In our model these residues are distant from the metal center and in general changes in this area of the peptide do not make a large difference in the selectivity that is obtained. One would expect changes at the turn residues to have a significant impact. In looking at a series where residue Yyy is the only residue varied, Gly and D-Phg gave consistently lower selectivities. In the ultimate test of this idea a derivative of the ligand that gave the highest selectivity, (Ac-D-Phg-Pps-Pro-D-Val-Pps-D-Leu-resin) was made in which Val was replaced with Aib. Aib should maintain secondary structure while positioning a methyl group at the face of the transition metal (Figure 2, **7**). This peptide (Ac-D-Phg-Pps-Pro-Aib-Pps-D-Leu-resin) gave significantly lower selectivity, 24% ee.

To test if the turn motif was responsible for the observed selectivity, a 40-member library was synthesized that contained more severe alterations to the sequences. This was done by deleting or substituting Gly for either proline or the D-amino acid. A second significant change was positioning a single amino acid between the phosphine amino acids and the β-turn. These substitutions resulted in complexes that gave essentially no selectivity. *These types of substitutions were the only changes in the basic ligand that consistently gave selectivities below 30% ee.* Peptides containing only one phosphine were also tested. These ligands were included to determine if the bis-chelation was essential. These ligands not only gave low selectivities but also proceeded with low conversions.

(23) The selectivities determined in the initial library appear to be slightly higher than later numbers because of changes in the method used to determine the ee. It is important to note that the trends in the initial data are identical to subsequent data. The best ligand in the initial screen is the best ligand in all subsequent testing. The superior method for the determination of the selectivity is the method of Evans: Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 2994−2995.

Scheme 3



8 57% *ee* **9** 48% *ee* **10** 48% *ee*

One of the original goals of this approach was to determine if it was possible to accurately screen the library members without resulting to removing the ligands from the solid support. This proved to be the case. When one of the best ligands (Ac-D-Phg-Pps-Pro-D-Val-Pps-D-Leu-NH_2) was removed from the solid support and purified by HPLC, it coordinated palladium and catalyzed the allylation with the same selectivity as when it was on the support (74% ee). This is an important observation since it indicates that this method allows for the direct screening of libraries while they are attached to the support they were synthesized on. Additionally, this is indirect evidence that the structure of these β-turn peptides is the same on the support as in solution. In an attempt to probe the optimal selectivity of these ligands, while attached to the synthesis support, the peptide found to give the best selectivity (D-Phg-Pps-Pro-D-Val-Pps-D-Leu) was tested at −20 °C. At that temperature the palladium complex of that ligand was found to give 85% ee of one enantiomer.

The most selective catalyst for the addition of dimethyl malonate to cyclopentenyl acetate was tested to determine its selectivity with other substrates (Scheme 3). The selectivies with these substrates was significantly lower than that obtained with the cyclopentenyl acetate (**3**). This may be expected since the ligand used on those substrates was optimized for cyclopentenyl acetate. This points out one of the goals of this research. It will often not be possible to have a catalyst that runs on many substrates with high selectivity. When this is the case, a system that allows for the rapid optimization of a specific catalyst for a specific substrate will be potentially useful.

In this work we have shown that phosphine-containing β-turn ligands are effective as catalysts for asymmetric catalysis while attached to the polymer support they were synthesized on. The results obtained with the catalysts immobilized appear to translate to results obtained with the same ligands in solution. This work illustrates the potential of this approach in the development of new peptide-based phosphine ligands by a parallel approach. We are currently synthesizing derivatives of *cis*-hydroxyproline with the goal of developing ligands with higher selectivities as well as catalysts for other reactions.

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Supporting Information Available: Sample procedures and full results from all the libraries synthesized (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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