JOC*Article*

Catalysis with Phosphine-Containing Amino Acids in Various "Turn" Motifs

Anton Agarkov,[†] Scott J. Greenfield,[†] Takahiro Ohishi,[†] Scott E. Collibee,[†] and Scott R. Gilbertson*[,‡]

Department of Chemistry, Washington University, One Brookings Drive, Saint Louis, Missouri 63130-4899, and Chemical Biology Program, Pharmacology and Toxicology, The University of Texas Medical Branch, 301 University Boulevard, Galveston, Texas 77555-0650

srgilber@utmb.edu

Received May 27, 2004

We have been actively involved in the development of parallel approaches for the discovery of phosphine ligands. Our approach has been based on the incorporation of phosphine-containing amino acids into peptide sequences that are designed to have stable secondary structures. We have examined helical and turn secondary structures and have reported that alkylation of cyclopentenyl acetate with dimethylmalonate can be catalyzed in high enantiomeric excess (ee) with a β-turn-based ligand. The importance of the peptide secondary structure was demonstrated through the synthesis of a series of peptide ligands where the nature of the turn-forming residues was probed. Additionally, other turn-forming units and a variety of different phosphine-containing amino acids have been examined for their ability to control the selectivity of the allylation reaction. This paper reports the results obtained through the examination of different turn motifs as well as different phosphine substitutions on the "best" turn sequence, Pps-Pro-D-Xxx-Pps.

Introduction

We have utilized phosphine containing β-turn peptide secondary structures to control the selectivity of palladium-catalyzed allylation. [It is important to note that β-turn structures have been use successfully in asymmetric nucleophilic catalysis by Miller.[9−12] That work represents an excellent example of the power of using peptide chemistry in assembly and screening of libraries of catalysts for asymmetric catalysis.] Figure 1 illustrates where substitutions have been made on the β-turn systems. A series of peptides were synthesized containing a variety of different phosphine-containing amino acids (R^a). Libraries were screened where the stereochemistry and properties of the residues at the ends of the peptide were varied (R^d and R^e), and turns containing derivates of proline, where the 4-position has different substituents (R^b), were also examined. A third variation where a variety of different D-amino acids (R^c) were used was tested. In addition to these modifications of the basic Pps-turn-Pps motif, several different turn-forming elements have been tested including cyclic peptides.

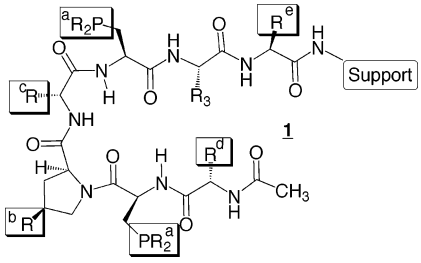


FIGURE 1. Boxed sections will be varied, and the resulting ligands will be screened for selective catalysis.

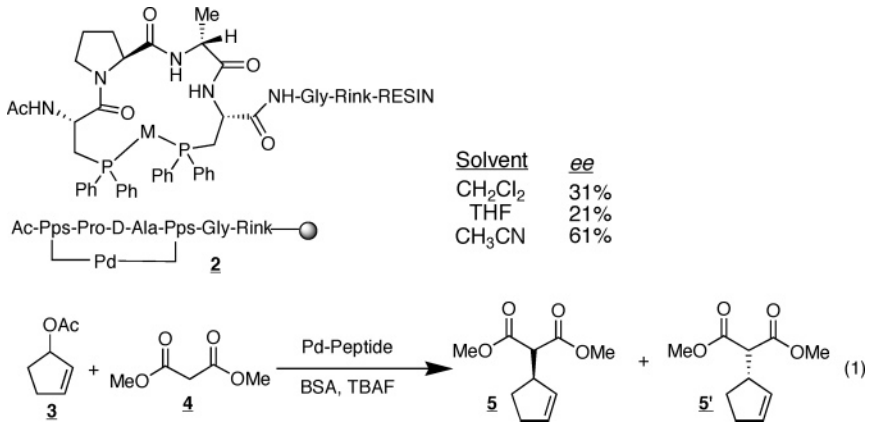
Importance of β-Turn Secondary Structure. Our initial goal was to synthesize libraries of peptide-based phosphine ligands. These libraries were based on the known β-turn-forming unit proline-D-amino acid.[13,14] Prior to the synthesis of the libraries, a single peptide was synthesized (**2**), characterized, and tested for its ability to catalyze the desired reaction (Scheme 1). At that time, a study of three different solvents was performed as well. This first experiment provided a peptide

[†] Washington University.
[‡] The University of Texas Medical Branch.

(1) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481−4482.
(2) Gilbertson, S. R.; Wang, X. *J. Org. Chem.* **1996**, *61*, 434−435.
(3) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475−6478.
(4) Gilbertson, S. R.; Wang, X. *Tetrahedron* **1999**, 11609−11619.
(5) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522−6523.
(6) Gilbertson, S. R. In *Progress in Inorganic Chemistry*; Karlen, K. D., Ed.; John Wiley & Sons: New York, 2001; Vol. 50, pp 433−471.
(7) Greenfield, S. J.; Gilbertson, S. R. *Synthesis* **2001**, 2337−2340.
(8) Greenfield, S. J.; Agarkov, A.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 3069−3072.
(9) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.
(10) Sculimbrene, B., R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125−10126.
(11) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134−2136.
(12) Sculimbrene, B., R.; Morgan, A., J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*.
(13) Imperiali, B.; Kapoor, T. M. *Tetrahedron* **1993**, *49*, 3501−3510.
(14) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182−3188.

10.1021/jo049103g CCC: $27.50
Published on Web 10/21/2004

SCHEME 1



that catalyzed the alkylation of cyclopentenyl acetate in 61% ee when acetonitrile was used as the solvent. This promising initial result was obtained while the catalyst was attached to the support on which it was synthesized. This is significant since the goal was to screen the library members while they were attached to the polymer support.

Next, a library of 96 ligands was synthesized (see the Supporting Information for sequences) and screened for its members' ability to selectively catalyze this allylation reaction (see Figure 3). The library was designed to have the basic phosphine-turn-phosphine motif with the elements of diversity being the amino acids on either end of the sequence and the side chain of the D-amino acid (Figure 2 R^c, R^d, and R^e). 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 substitution 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. Amino acids placed in the Xxx and Zzz locations were Ala, Gly, Phe, Glu, Cys, Ser, Lys, and Tyr 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. Palladium was coordinated to these ligands, and catalysis was performed. Initially, the ligands were screened while attached to the polymer support on which they were synthesized. The selectivities obtained with this library ranged from 34% ee for the lowest to 80% ee in the case of the highest selectivity. There were 77 members of the library that gave 60% ee or greater selectivity. While the selectivities obtained with these supported ligands were

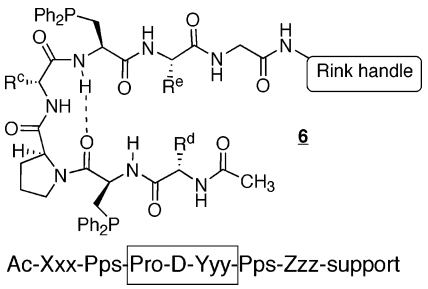


FIGURE 2. Pro-D-amino acid dimer the first libraries were based on.

quite good, with one ligand giving 80% ee, there was no substitution at the sites of diversity that provided a clear advantage over most other substitutions.

At this time, it was decided to determine if the phosphine-turn-phosphine motif was responsible for the observed selectivity or if any random sequence containing chiral amino acids with phosphine in their side chain would provide similar selectivity. A second 40-member library was synthesized that contained more severe alterations to the sequences (exact sequences are provided in the Supporting Information). The most significant trend observed with this library was introducing changes that disrupted the turn-forming unit. This was done by deleting or substituting Gly for either proline or the D-amino acid (Figure 4, red box). A second significant change was positioning a single amino acid between the phosphine amino acids and the β-turn (Figure 4, yellow box). These two sets of substitutions were the only changes in the basic ligand that consistently gave selectivities below 30% ee. In the initial library the majority of the substitutions made were on the ends of the peptide and not at the turn where the transition metal appears to be facing. As can be seen in Figure 4, the most significant substitutions are at the turn. With that in mind, a series of changes at the turn section were performed.

Ultimately, it is important that results obtained with the complexes attached to the polymer support correlate to results obtained with the complexes in solution. Without this it would not be possible to study the structure of the successful catalysts and make decisions as to how to focus the next libraries. In the case of the β-turn derived ligands, this correlation was observed. Upon removal of the most selective ligands from the polymer support it was found that their selectivity in solution was nearly the same as when they are immobilized (80% ee on support 85% ee in solution). This indicates that in the case of short structured peptides, groups of complexes can be screened while they are attached to the resin on which they are synthesized.

Substitutions at Proline. Given the relatively small effect observed when making changes at end of the turn structure, it was decided to make a series of changes at the turn-forming residues. The MOM- and TBDMS-protected derivatives of hydroxyproline (**8**−**11**) were introduced instead of proline in the i+1 position. Additional diversity was generated by removal of the

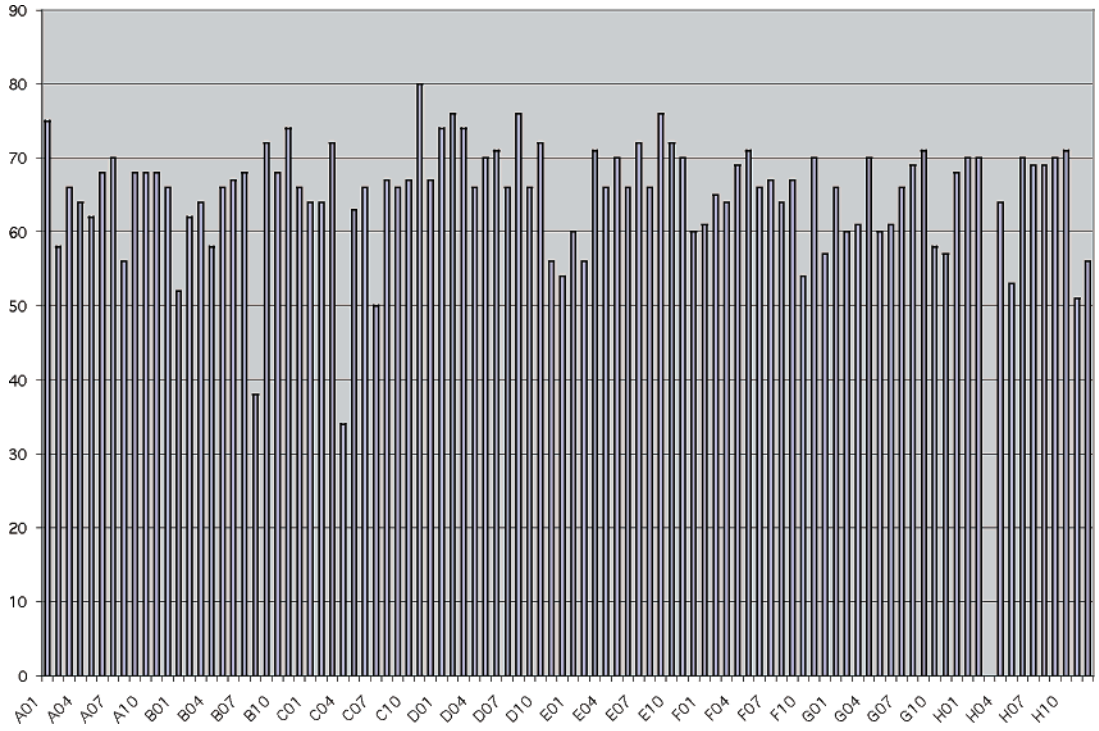


FIGURE 3. Results from the first 96-member library synthesized, based on the Pps-Pro-D-amino acid-Pps motif. The identity of the library members is reported in the Supporting Information

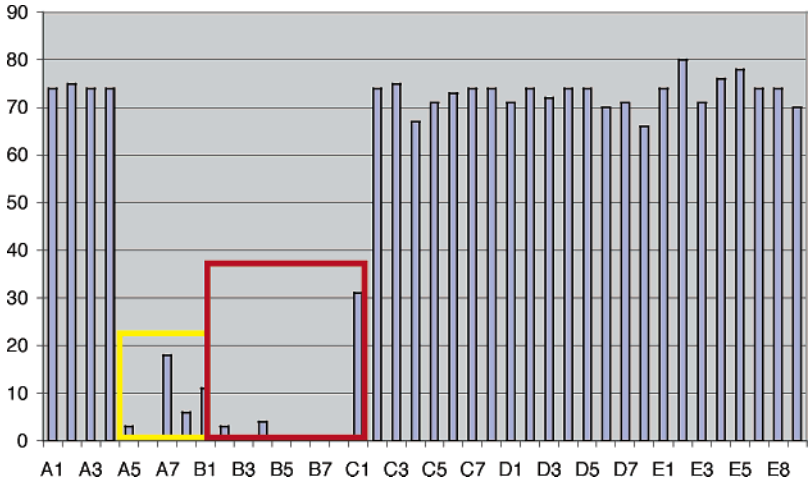


FIGURE 4. Results from the library where some members differed from the basic phosphine-turn-phosphine motif. The identity of the library members is reported in the Supporting Information.

t-BuMe$_2$Si groups with fluoride anion after completion of solid-phase peptide synthesis (**12**, **13**). Screening of the resulting six peptides was conducted in two separate experiments. In every case but one, catalysis with these ligands resulted in a decrease in selectivity. The best selectivity was achieved with unprotected *trans*-Hyp (**12**), which was the same ee obtained using the original peptide **7**. Since peptide **12** represents the least significant perturbation from the base ligand **7** it appears that for this reaction changes at this site will not result in greater selectivity (Figure 5).

Different "Turn"-Forming Motifs. Our initial work, examining the use of peptides that possess the Pro-D-Xxx sequence between the two phosphine ligands, demonstrated that upon coordination the metal is presented in a conformation where it is in the vicinity of the proline and the D-amino acid. This makes the interaction of the substrate with these residues important in determining the selectivity of the product. Because the orientation of the metal is toward the turn (Figure 7), two other motifs known to form turn-type structures were examined. Since this is the important region of the peptide other turn-forming units may alter the specificity of the catalyst with different substrates. It has been shown by Gellman that homochiral depsipeptides, which contain L-acids, tend to form β-turn and hairpin secondary structures.[15,16]

(15) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4105−4106.
(16) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975−6985.

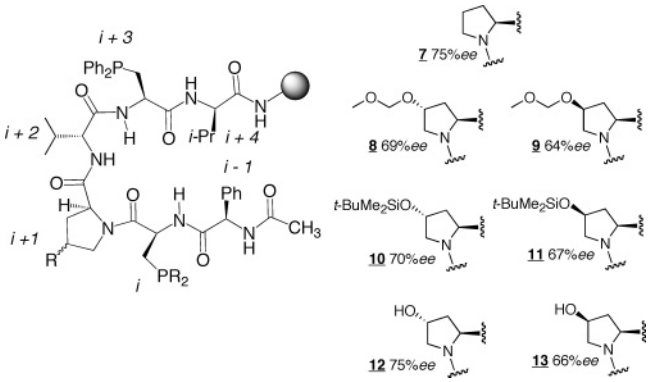
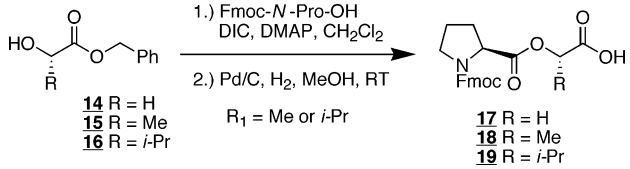


FIGURE 5. Selectives observed in reaction (1) with different proline derivatives.

SCHEME 2



Additionally, the Gellman laboratory has shown that heterochiral dinipecotic acid segments promote antiparallel sheet interactions.[17−22] Given that we have been able to use the β-turn secondary structure to control the selectivity of palladium-catalyzed allylations we decided to examine these sequences.

The possibility of using depsipeptides in asymmetric catalysis was investigated. Dimers of proline and glycolic, lactic, and leucic acids were prepared (Scheme 2) and incorporated into the middle of amino acid tetramers. This collection of peptides contained homochiral and heterochiral sequences (Table 1, entries 1−6). In addition, three peptides with racemic diphenylphosphinoserines were prepared. The resulting nine depsipeptides were tested as ligands in the palladium-catalyzed alkylation of cyclopentenyl acetate. The palladium catalysts made from the nine depsipeptides catalyzed the alyllation with high conversion but provided racemic product. As a control, two examples of analogous peptide sequences, where the Pro-ester linkage was replaced with an amide (Table 1, entries 10 and 11), were tested. In both cases, those examples provided selectivites comparable to what we have obtained with other Pps-Pro-D-Xxx-Pps peptides. Apparently, the planar amide bond generates a significantly different environment than the ester bond and is at least partially responsible for the selectivities we observe in the Pro-D-Xxx systems.

As noted above, the heterochiral dinipecotic acids segments promote antiparallel sheet interactions.[17,21]

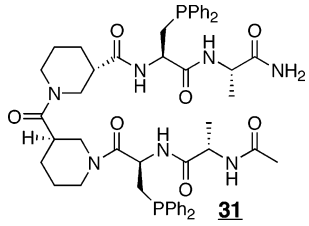
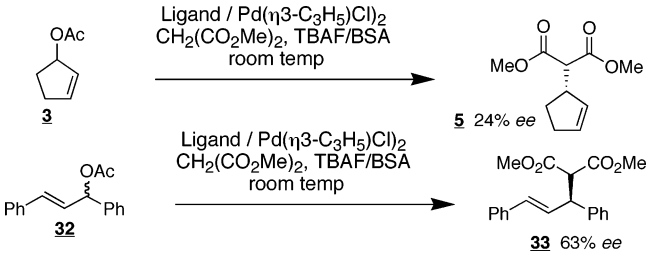


FIGURE 6. Heterochiral dinipecotic acid peptide ligand Ac-Ala-Pps-*R*-Nip-*S*-Nip-Pps-Ala-NH_2.

SCHEME 3



With this in mind we decided to examine what level of selectivity we would obtain with a peptide motif that positioned Pps on either side of this element. Ac-Ala-Pps-(R)-Nip-(S)-Nip-Pps-Ala-NH_2 (**31**) (Figure 6) was chosen as a model peptide on the basis of Gellman's studies.[18−22] The peptide (**31**) was synthesized on solid support by the standard Fmoc protocol, and the crude peptide was purified by preparative HPLC to afford **31** as a white solid.

The reaction of two allyl substrates and dimethylmalonate were examined by the TBAF/BSA method developed in our laboratory. The reaction with cyclopentenyl acetate was found to give poor selectivity (24% ee). However, catalyst **31** gave 63% ee in the reaction with diphenylallyl acetate **32** (Scheme 3). In the Pro-D-Yyy system (**6**), linear allyl acetates such as 1,3-diphenylallyl acetate do not undergo catalytic alkylation. Presumably this is due to the pocket formed by the turn being too small to accommodate the extended palladium complex. The Nip-Nip β-turn is more open and the metal is farther away from the two residues forming the turn. Therefore, this ligand allows the formation of the extended palladium allyl complex and consequently is an active catalyst for linear allyl acetates such as diphenylallyl acetate.

As can be seen in Figure 7, the gross structure of the three types of turning forming sequences we have examined is significantly different. The (*R*)-Nip-(*S*)-Nip sequence (**36**) is significantly more open than the sequence Pro-D-amino acid turn (**34**) originally examined. As a consequence, substrates that will not fit into the pocket of **34** are catalyzed by the palladium complex **36**. While the static structure of **35** resembles the structure of **34**, the substitution of an ester for an amide apparently alters either the structure or its stability significantly since palladium complexes of **35** catalyze the allylation reaction with no selectivity. Given the relatively low selectivity obtained in the allylation with cyclopentenyl acetate and 1,3-diphenylallyl acetate, we decided not to investigate the use of either prolactyl turns or the Pps-(*R*)-Nip-(*S*)-Nip-Pps systems further in the allylation reaction.

(17) Chung, Y. J.; Christianson, L. A.; Stanger, H. E.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1998**, *120*, 10555−10556.
(18) Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 9035−9037.
(19) Huck, B. R.; Fisk, J. D.; Gellman, S. H. *Org. Lett.* **2000**, *2*, 2607−2610.
(20) Arnold, U.; Hinderaker, M. P.; Nilsson, B. L.; Huck, B. R.; Gellman, S. H.; Raines, R. T. *J. Am. Chem. Soc.* **2002**, *124*, 8522−8523.
(21) Chung, Y. J.; Huck, B. R.; Christianson, L. A.; Stanger, H. E.; Krauthauser, S.; Powell, D. R.; Gillman, S. H. *J. Am. Chem. Soc.* **2000**, *122*, 3995−4004.
(22) Lai, J. R.; Huck, B. R.; Weisblum, B.; Gellman, S. H. *Biochemistry* **2002**, *41*, 12835−12842.

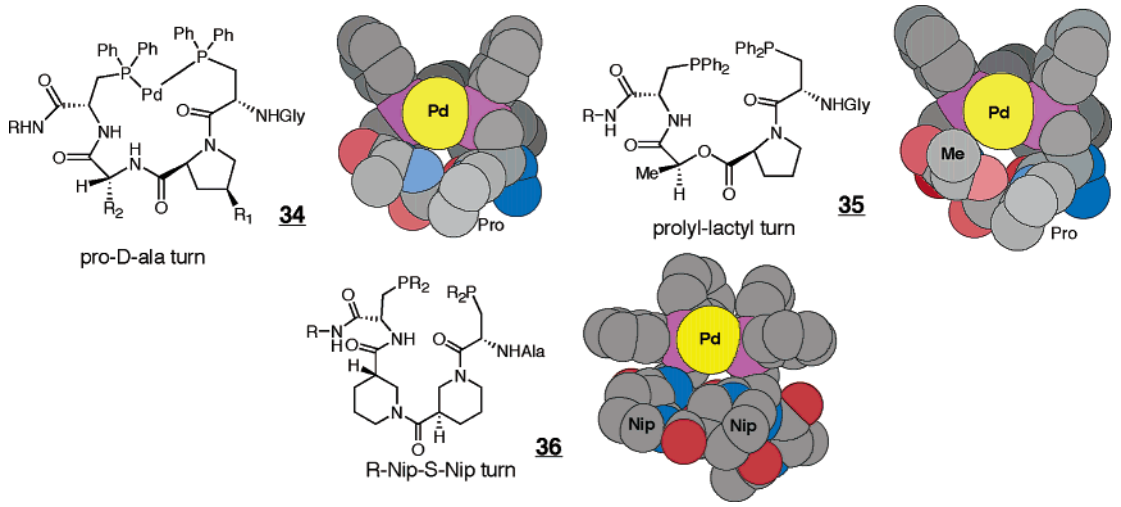
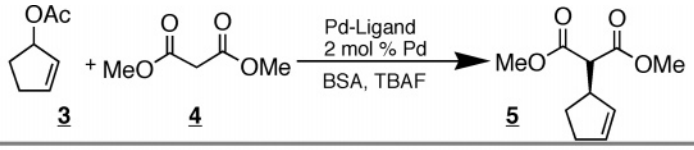
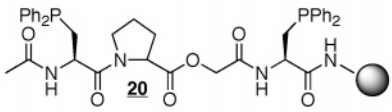
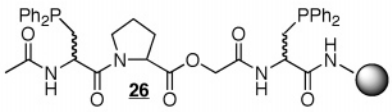
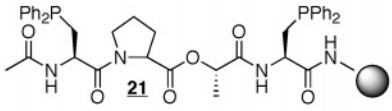
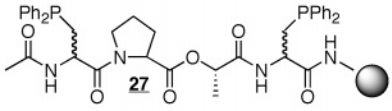
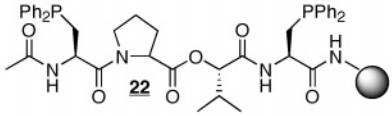
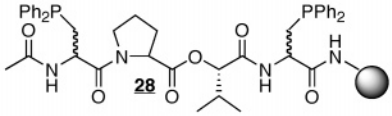
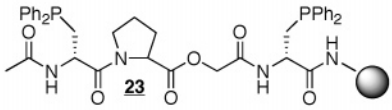
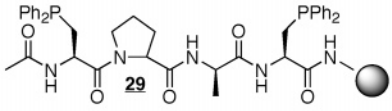
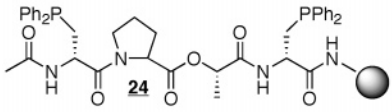
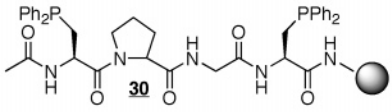
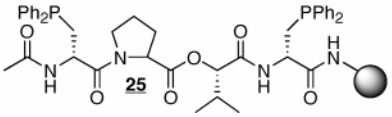


FIGURE 7. Space-filling representations of the three turn-based phosphine−palladium catalysts.

TABLE 1. Hydroxy acids in the *i*+2 Position



Entry		ee,%	Entry		ee,%
1		0	7		0
2		0	8		0
3		0	9		0
4		0	10		74
5		0	11		55
6		0			

Cyclic Peptide Ligands. In an attempt to optimize the selectivity of the initial β-turn system, we decided to test a series of cyclic peptides that contain the basic Pps-Pro-D-Xxx-Pps sequence. A small six-member library was synthesized to examine the possibility of improving the existing selectivity by using more rigid cyclic structures (Figure 8). The cyclic peptides contained glutamic acid in the first position coupled to the same six amino acid

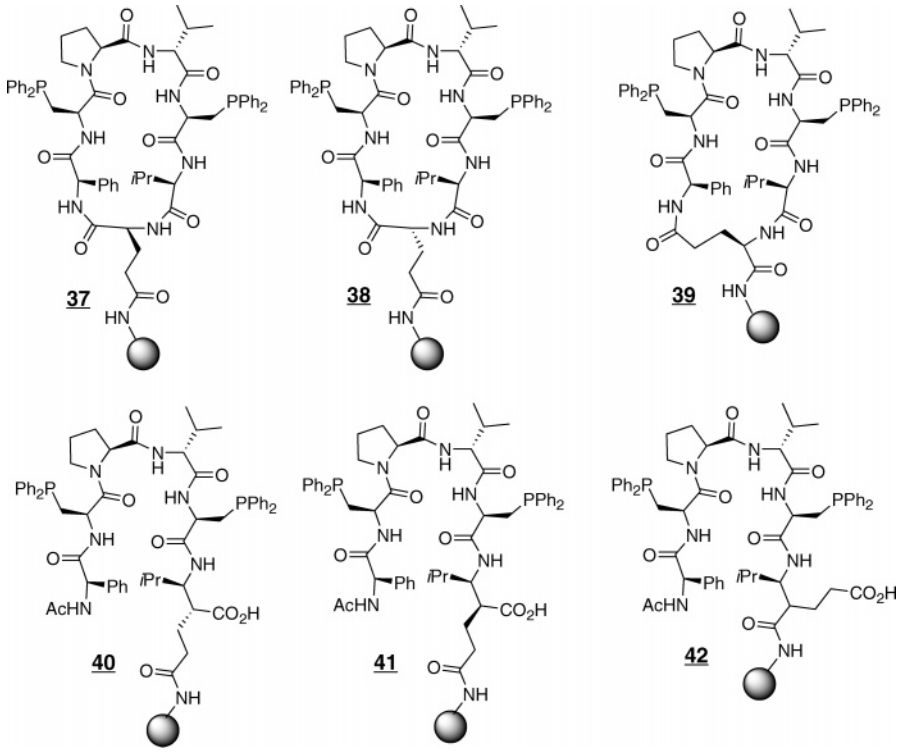
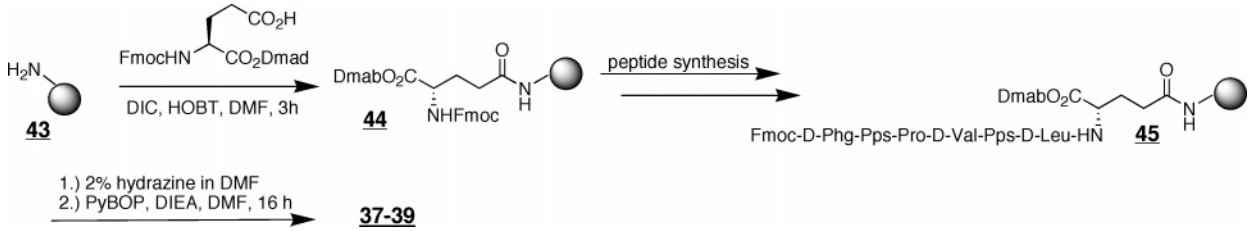


FIGURE 8. Three cyclic peptides examined and their open-chain analogues.

SCHEME 4

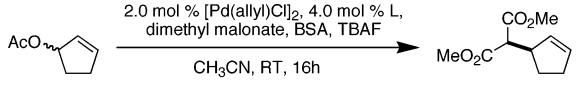


sequence that form the β-turn motif. The peptides were prepared using quasi-orthogonally Dmab-protected derivatives of glutamic acid (Scheme 4). The Dmab group is practical because it is stable toward 20% piperidine in DMF, the conditions for Fmoc deprotection, but can be removed using 2% hydrazine in DMF. The cyclization was done using the α-carboxyl group (L- and D-Glu; **37** and **38**) and the γ-carboxyl group (L-Glu; **39**) of glutamic acid. To monitor the cyclization step and for comparison with the cyclic counterparts, corresponding linear analogues (**40**−**42**) were prepared as well.

The peptides were used as ligands for the palladium-catalyzed reaction of cyclopeny acetate and dimethyl malonate anion. All reactions proceeded to completion and gave similar ee's (Table 2). It is interesting to note that the three cyclic peptides tested gave lower selectivities than the corresponding "linear" peptide. Presumably, this is due to the cyclic constraint altering the structure of the turn-forming residues.

The examined cyclic structures were rather flexible. A plan to synthesize smaller more rigid cyclic peptides failed due to the inability to systematically synthesize small libraries. It is known that the rate of cyclization of short peptide sequences is dependent on the stereochemistry of the residues. While it is possible to synthesize individual peptides, this problem prevents the synthesis of small cyclic peptides in a parallel manner.

TABLE 2. Results for Cyclic Peptides

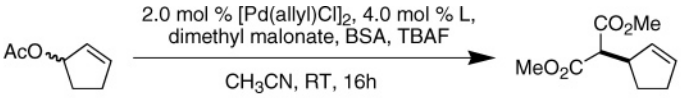


3 **5**

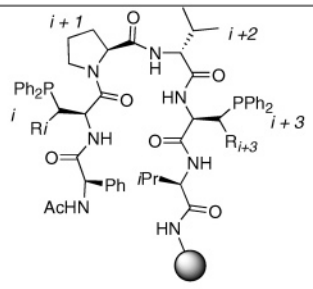
Ligand	Cyclic			Linear		
	37	**38**	**39**	**40**	**41**	**42**
ee, %	68	66	71	73	71	69

Modification of the Phosphine Amino Acid: Substitution at the β-Carbon. The phosphine group is attached to the peptide by a CH_2 group (β-carbon), which can be used to introduce another source of chirality to the system. Replacement of one of the hydrogens of this CH_2 group with an alkyl or aryl group will position a chiral center next to the phosphine and potentially control the conformation of the metal ligand complex. These new chiral centers can either complement or cancel the existing chirality conferred by the peptide. With this issue in mind all eight possible diastereomeric combinations were synthesized and screened for their ability to

TABLE 3. Pps(β-Ph) vs Pps for the Reaction of Cyclopentenyl Substrate



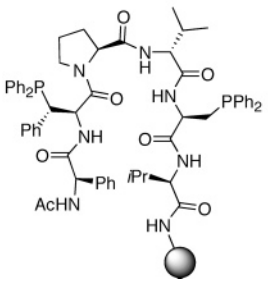
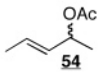
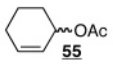
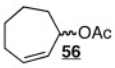
3 **5**



R_i \ R_{i+3}	Pps	Pps(β-*R*-Ph)	Pps(β-*S*-Ph)
Pps	(**7**) 76	(**46**) –17[a]	(**47**) –2[a]
Pps(β-*R*-Ph)	(**48**) –17[a]	(**49**) –27[a]	(**50**) –3[a]
Pps(β-*S*-Ph)	(**51**) 78[a]	(**52**) –4[a]	(**53**) 31[a]

[a] ee, %; positive values correspond to the *R*-enantiomer (shown), negative to the *S*-enantiomer.

TABLE 4. Ligand 51 in the Reaction with Other Substrates

Ligand	Substrate	Conversion, %	ee, %
	 **54**	~ 75	53
	 **55**	~ 75	46
	 **56**	~ 65	35

control the selectivity of the allylation reaction (Table 3). The results for this experiment varied dramatically. Out of eight new ligands (**46**−**3**), six gave the opposite enantiomer as the major product in low ee (**46**−**50** and **52**). The only sequence to provide high selectivity (**51**) was with Pps(β-*S*-Ph) in the *i* position and Pps in the *i*+3 position.

Since the palladium complex of peptide **51** catalyzed the reaction with cyclopentenyl acetate with good selectivity, it was tested on three other substrates (**54**, **55**, and **56**) to determine if it may be more selective with these molecules than the standard ligand **7** (Table 4). The conversion at 16 h with ligand **51** was lower than those obtained with **7**. This could be due to an increase in the steric congestion around the metal. In the case of cyclic substrates **55** and **56**, the selectivities were lower than those obtained with ligand **7**. However, with the very difficult substrate 1-methylbut-2-enyl acetate (**54**) the selectivity was slightly higher (53% ee vs 48% ee). While the substitution of a phenyl group on the methylene next to the phosphine influenced the reaction selectivity, in most cases it resulted in lower selectivity than was obtained with the parent ligand **7**.

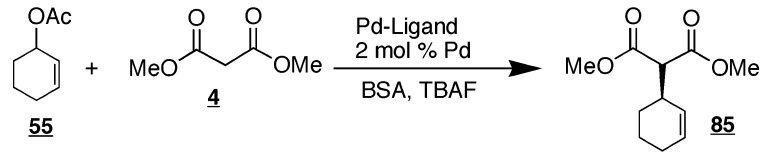
Modification of the Phosphine Amino Acid: Substitution at Phosphorus. The decrease in selectivity observed with ligands possessing a group on the β-carbon indicates that substitutions in this area of the ligand can have a significant effect on the catalyst. With this in mind, a different modification at this region was investigated. The other location that can be modified in these ligands is at the other groups attached to the phosphine. Our best route to the required amino acids allows for the facile synthesis of amino acids with a wide variety of different alkyl and aryl groups attached to phosphorus.[7] With these phosphine amino acids in hand, a library was synthesized using the aromatic groups on the phosphine as the source of diversity. Table 5 contains the results from the study of a small library of β-turn type peptides with various aromatic groups attached to the phosphine moiety. The starting point for the library was Ac-D-Phg-Pps-Pro-D-Ala-Pps-D-Leu-support, a sequence that provided moderate success previously. In general, it appears that when the phosphine next to proline is larger, the catalyst provides higher selectivity. There also appears to be a preference for symmetrical groups on the phosphine, with 3,5-dimethyl-substituted phenyl providing the highest selectivity (entries 5 and 6). The library also contains examples where the phosphine amino acid was chiral at phosphorus. These examples provided some of the lowest selectivities in the study (entries 16−19).

After determining the "best" phosphine containing amino acids for the ligand, the other amino acids in the sequence were examined (Table 6). The turn-forming motif was retained by maintaining Pro or Oic and a D-amino acid at the critical *i*+1 and *i*+2 positions. Substitution of amino acids away from the metal had a negligible effect on the selectivity of the catalyst, while substitution of D-Val in the *i*+2 position increased the selectivity slightly (86% ee).

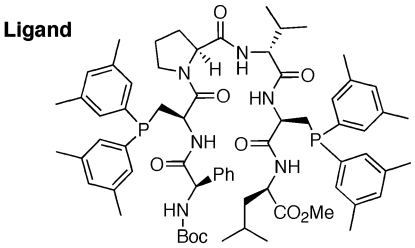
Following the optimization of the ligand system, the reaction conditions were examined. Upon examining a number of solvents (DMF, THF, acetone, benzene, and acetonitrile), acetonitrile was found to be the solvent that provided the highest selectivity with the polymer bound catalyst. At 0 °C in acetonitrile, ligand **76** provided the product in 95% yield and 88% ee.

The synthesis of peptides on solid support generally provides products of high purity. However, there was concern that small amounts of impurities could, upon coordination to the metal, provide catalysts with significantly greater activity and poorer selectivity than the desired catalyst. To test this concern, the best ligand (**76**)

SCHEME 5

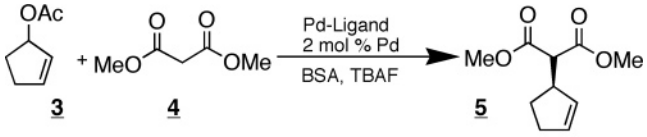


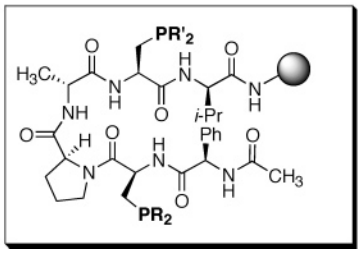
On support 94% yield, 83% *ee* THF solvent
In solution 89% yield, 88% *ee* THF solvent



84 Ac-Gly-Xps-Pro-D-Ala-Xps-Gly-NH_2

TABLE 5. Catalysis with Various Phosphine Amino Acids[a]





entry	compd	R	R′	yield[b] (%)	ee[c] (%)
1	**57**	Ph	Ph	76	67
2	**58**	2,5-xyl	2,5-xyl	78	20
3	**59**	2,5-xyl	Ph	86	55
4	**60**	Ph	2,5-xyl	93	31
5	**61**	3,5-xyl	3,5-xyl	88	77
6	**62**	3,5-xyl	Ph	96	81
7	**63**	Ph	3,5-xyl	91	64
8	**64**	1-Nap	1-Nap	86	15
9	**65**	1-Nap	Ph	93	64
10	**66**	Ph	1-Nap	88	17
11	**67**	1-Nap	2-Nap	91	57
12	**68**	2-Nap	1-Nap	93	28
13	**69**	2-Nap	2-Nap	85	70
14	**70**	2-Nap	Ph	91	73
15	**71**	Ph	2-Nap	91	59
16	**72**	1-Nap/Ph	1-Nap/Ph	88	55
17	**73**	Ph/1-Nap	Ph/1-Nap	91	14
18	**74**	Ph/1-Nap	1-Nap/Ph	88	32
19	**75**	1-Nap/Ph	Ph/1-Nap	68	30

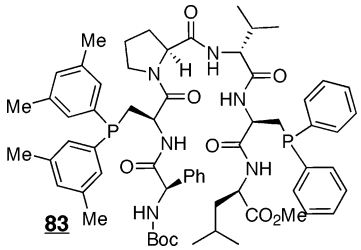
[a] All ligands where synthesized and screened on the Synphase system from Mimotopes. Reactions were run at 0 °C to rt, using *N,O*-bis(trimethylsilyl)acetamide, TBAF, and dimethylmalonate. [b] Isolated yield. [c] Enantiomeric excess was determined by ^{1}H NMR analysis using [Eu(hfc)$_3$] shift reagent.

TABLE 6. Ac-Www-Xps[a]-Xxx-Yyy-Pps[b]-Zzz Support

	compd	Www	Xxx	Yyy	Zzz	ee[e] (%)
1	**76**	D-Phg	Pro	D-Val	D-Leu	86
2	**77**	D-Phg	Oic	D-Ala	D-Leu	79
3	**78**	D-Ala	Pro	D-Ala	D-Phg	82
4	**79**	D-Phg	Pro	D-Ala	D-Ala	82
5	**80**	D-Phg	Pro	D-Ala	D-Phg	81
6	**81**	D-Ala	Pro	D-Ala	D-Ala	79
7	**82**	D-Phg	Pro	D-Tle	D-Leu	42
8	**62**	D-Phg	Pro	D-Ala	D-Leu	81

[a] Xps represents phosphine amino acid with 3,5-xylene on phosphine. [b] Pps represents phosphine amino acid with phenyl on phosphine. [c] All reactions were run at 0 °C to rt using *N,O*-bis(trimethylsilyl)acetamide, TBAF, and dimethyl malonate. [d] Isolated yield. [e] Enantiomeric excess was determined by ^{1}H NMR analysis using [Eu(hfc)$_3$] shift reagent.

TABLE 7. Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe (83)



83

entry	solvent	*T* (°C)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	0 to rt	82	88
2	toluene	0 to rt	89	89
3	acetone	0 to rt	91	88
4	CH_3CN	0 to rt	90	85
5	THF	0 to rt	92	90
6	THF	0	91	95
7	THF	−20	90	92
8	THF	−30	85	89
9	DMF	−45	92	85

[a] All reactions were run using *N,O*-bis(trimethylsilyl)acetamide, TBAF, and dimethyl malonate. [b] Isolated yield. [c] Enantiomeric excess was determined by^{1}H NMR using [Eu(hfc)3] shift reagent.

was synthesized in solution and purified by chromatography (**83**). Reaction of peptide **83** in acetonitrile provided a catalyst that gave the addition product with comparable yield and selectivity to the reaction in acetonitrile when the catalyst was immobilized on the synthesis support (90% yield, 85% ee vs 91% yield and 86% ee). Further study of the conditions revealed that when the catalyst is dissolved in solution the best solvent appears to be THF rather than acetonitrile. Reaction in THF at 0 °C provided the product in good yield and with excellent selectivity (Table 7, entry 6, 91% yield, 95% ee). *This selectivity is comparable to the best ligands known for this reaction.*[23−29]

(23) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905−7920.
(24) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
(25) Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99−102.
(26) Trost, B. M. In *Catalytic Asymmetric Synthesis*; Ojima, T., Ed.; Wiley-VCH: New York, 2000; p 593.
(27) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919−2920.
(28) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047−3050.

When the best ligand for 3-acetoxycyclopentene, Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe, was used with the 3-acetoxycyclohexene (**55**), the selectivity was 76% ee with the ligand on support and 81% ee with the ligand in solution. Minimal optimization of this system ultimately provided Ac-Gly-Xps-Pro-D-Ala-Xps-Gly-NH_2 (**84**) as the best ligand for this system (83% ee on support and 88% ee in solution, Scheme 5).

Conclusion

In his original paper on the rhodium-catalyzed hydrogenation by chiral phosphine rhodium complexes, Knowles states that phosphine complexes have "the advantage that the structure of the catalyst ligands can be varied according to the particular unsaturated substrates in order to achieve maximum asymmetric yield".[30] Since that original paper, hundreds of chiral phosphines have been synthesized but there have been no general methods developed to facilitate the synthesis and screening of phosphine complexes. Our work illustrates the need for methods that allow the rapid synthesis of diverse ligand sets. In the case of palladium-catalyzed allylation with cyclic substrates, when peptide-based ligands are used, β-turn secondary structure is critical for obtaining high selectivity. The example in Scheme 5 illustrates this as well. Simply changing from the cyclopentenyl system to a cyclohexenyl system requires new optimization of the ligand system. Consequently, the ability to rapidly synthesize diverse collections of ligands is important to accessing what Knowles originally viewed as a strength of catalysis with phosphine−transition-metal complexes, that the ligand−metal complex can be tuned for a reaction.

In addition to providing a facile approach for the synthesis of new ligands, a peptide-based approach to ligand synthesis provides an opportunity to use peptide secondary structure to control catalyst selectivity. While we have been successful applying the principles developed for the control and formation of β-turn secondary structures and using them in the development of asymmetric catalysts, it is important to note that given the large size of the phosphine side chains and the constraints that are imposed by coordination of a transition metal, the connection of our work to peptide folding issues is tenuous at best. The precise nature of the ligand's secondary structure is not certain, but it is clear that some secondary structure is necessary for selective catalysis. In situations where the secondary structure elements are varied, a profound change in catalyst selectivity is observed. Moving the metal-binding units one amino acid from the turn-forming residues decreases the observed selectivity to nearly zero. The replacement of the Pro-D-amino acid sequence with other dimers that are known to form turns also significantly decreases the catalysis selectivity. The simple substitution of an ester for an amide at the proline also results in a change from nearly 80% ee to zero. Clearly, the amide between the proline and the D-amino acid, which is remote to the metal in a through bond sense, has a profound effect on the selectivity of the transition metal. This along with structural work has led to a model that positions the metal near the turn-forming residues of proline and the D-amino acid.

The combination of the turn-forming residues and the groups on phosphorus provide a pocket. We are currently attempting to develop these types of ligands for other reactions such as the Heck reaction and metal-catalyzed cycloisomerizations. Additionally, systems that combine phosphines with other metal-binding groups are being developed.

Acknowledgment. This work was supported by NIH Grant No. R01 GM56490. We acknowledge the support of the Robert A. Welch Foundatio,n and Mimotopes, A Fisher Scientific Company, is acknowledged for materials support. KANEKA Corp. of Japan is acknowledged for support of Dr. Ohishi. We also gratefully acknowledge the Washington University High-Resolution NMR Facility, partially supported by NIH Grant Nos. RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by Grant No. NIHRR00954, for their assistance. Professor Samuel Gellman and Dr. Bayard Huck are acknowledged for communication of the procedure for the resolution of racemic nipecotic acid.

Supporting Information Available: Complete experimental details, compound characterization, identity of library members, and methods for the analysis of product enantiomeric purity. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049103G

(29) Gilbertson, S. R.; Xie, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 2750−2752.

(30) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, *22*, 1445−1446.