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High Asymmetric Induction with β-Turn-Derived Palladium Phosphine Complexes

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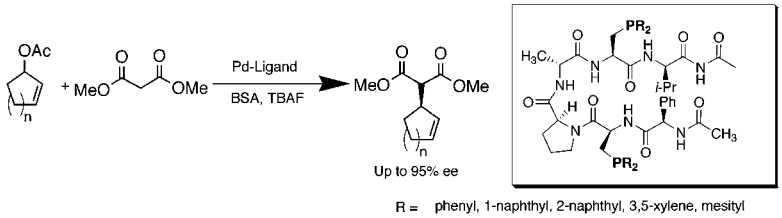
ABSTRACT



Work toward the development of a bisphosphine ligand system for the palladium-catalyzed addition to cyclic allyl acetates is reported. A parallel approach using phosphine-containing amino acids in conjunction with natural amino acids was used to develop a selective ligand system. The ligand system was examined while attached to the polymer support as well as in solution. Selectivites with the difficult substrate 3-acetoxycyclopentene of up to 95% ee are reported.

The parallel synthesis of phosphine ligands requires the use of reactions that proceed in good yield and with high selectivity. Our group has been involved in the development of parallel methods for the discovery of asymmetric catalysts. One of the approaches taken is based on solid-phase peptide synthesis.[1−8] Such an approach allows for the rapid development of selective catalysts for specific reactions or individual substrates. The utilization of solid-phase peptide chemistry in the synthesis of phosphine ligands requires the synthesis of phosphine-containing amino acids and the development of a system that allows for protection and deprotection of the phosphine moiety. We have reported such a system and have synthesized peptide-based phosphine ligands.[1−4] In addition, these ligands have been coordinated to rhodium and palladium and used in hydrogenation and allylation reactions.[6,7] While our initial results illustrated the feasibility of the approach, they provided catalysts with good but lower than desired selectivity. This paper reports the development of a peptide-based bisphosphine ligand that provides state of the art selectivity for the reaction of 3-acetoxycyclopentene with nucleophiles (Scheme 1 $n = 1$).

In the original design of peptide-based ligands, a sequence was chosen that was expected to form a β-turn secondary structure. Miller has used β-turn structures in the development of asymmetric acylation catalysts.[9−12] The plan was to use the ability to easily modify the amino acids on either end of the turn as the elements of diversity. That approach proved to be flawed in that, upon chelation, the metal is

(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.; Hoge, G. S.; Klug, C. A.; Schaefer, J. *Organometallics* **1996**, *15*, 4678−4680.
(5) Gilbertson, S. R.; Chen, G.; Kao, J.; Beatty, A.; Campana, C. F. *J. Org. Chem.* **1997**, *62*, 5557−5566.
(6) Gilbertson, S. R.; Wang, X. *Tetrahedron* **1999**, 11609−11619.
(7) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522−6523.
(8) Agardov, A.; Uffman, E. W.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091−2094.
(9) Copeland, G. T.; Jarvao, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784.
(10) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306−4307.
(11) Jarvo, E. R.; Copland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643.
(12) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.

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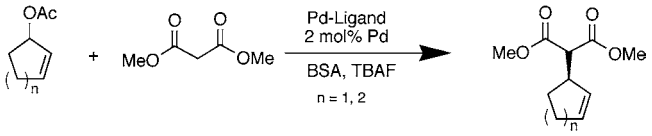
Scheme 1



positioned away from the carboxyl and amino ends of the turn and toward the residues critical for turn formation, proline and the D-amino acid (Figure 1). In an attempt to

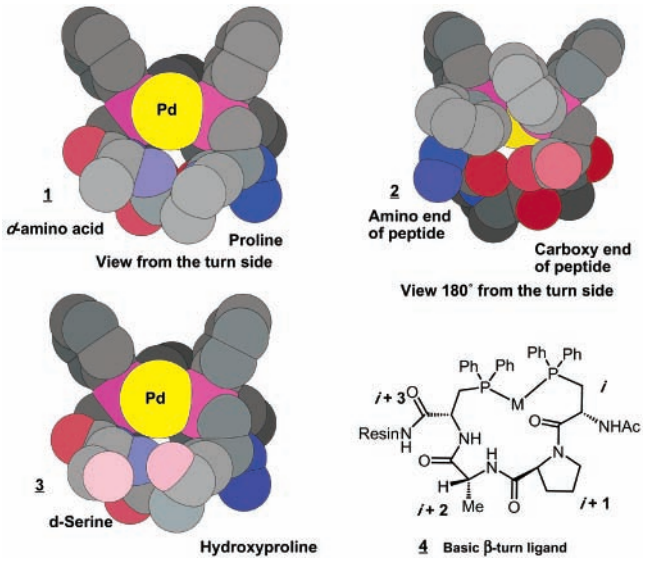


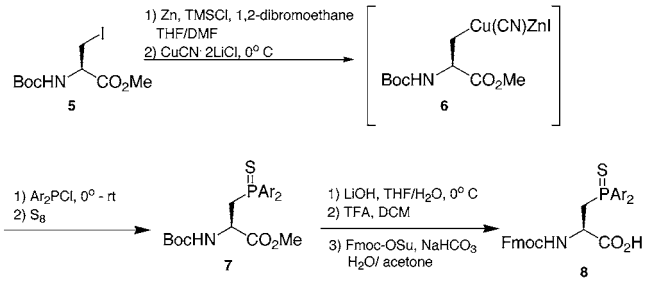
Figure 1.

exert direct control over the environment at the face of the transition metal, different turn-forming amino acids were placed in the critical $i + 1$ and $i + 2$ positions (**4**). A variety of hydroxyproline derivatives were examined along with different D-serine derivatives (**3**). In general, these changes resulted in a decrease in reactivity and selectivity. Another approach to influence the catalytic selectivity would be to make changes to the aromatic groups on the phosphine. While possible using the original synthesis of phosphine amino acids, the synthesis of a variety of amino acids would require a considerable amount of work.[1] To overcome this limitation, a new route to phosphine-containing amino acids had to be developed.[13]

The new route utilizes chemistry developed by Knochel (Scheme 2).[14,15] Commercially available iodo amino ester (**5**) was metalated with zinc and, following transmetalation with copper, was reacted with a chloro dialkyl or diaryl-phosphine. The phosphine was then protected as the phos-

(13) Greenfield, S. J.; Gilbertson, S. R. *Synthesis* **2001**, 2337−2340.
(14) Langer, F.; Puntener, K.; Sturmer, R.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 715−738.
(15) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2392.

Scheme 2



phine sulfide. Ester hydrolysis and exchange of Boc for Fmoc protection provided the desired amino acid in high yield. This method makes a wide variety of phosphine amino acids available. For the purposes of this study, a series of diaromatic phosphine amino acids were synthesized (Table 1) and examined.

Table 1.

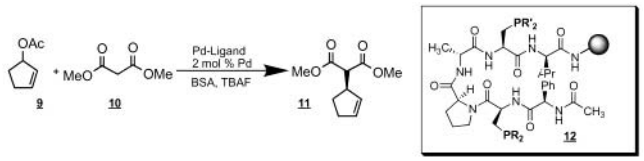
entry	Ar	yield[a,b] of **7**	yield[a,b] of **8**
1	phenyl	75% (**7a**)	80% (**8a**)
2	1-naphthyl	43% (**7b**)	43% (**8b**)
3	2-naphthyl	55% (**7c**)	61% (**8c**)
4	3,5-xylene	73% (**7d**)	73% (**8d**)
5	mesityl	40% (**7e**)	63% (**8e**)
6	phenyl, 1-naphthyl[c]	73% (**7f**)	65% (**8f**)
7	3,5-di-*tert*-butyl-4-methoxy phenyl	70% (**7g**)	95% (**8g**)
8	2,5-xylene	66% (**7h**)	40% (**8h**)

[a] Isolated yields. [b] Products were enantiomerically pure as determined by chiral HPLC. [c] Two diastereomers were separated by column chromatography.

With these phosphine amino acids in hand, a library was synthesized using the aromatic groups on the phosphine as the source of diversity. Table 2 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 in an earlier study. In general, it appears that when the phosphine next to proline was larger, the catalyst provided 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, as well as at the α-carbon. 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 3). 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

Table 2 [a]

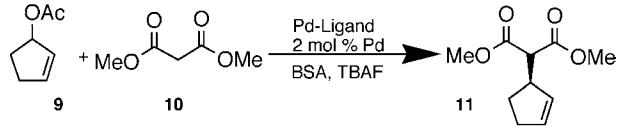


entry	compd	R	R′	yield[b]	ee[c]
1	**13**	Ph	Ph	76	67
2	**14**	2,5-xyl	2,5-xyl	78	20
3	**15**	2,5-xyl	Ph	86	55
4	**16**	Ph	2,5-xyl	93	31
5	**17**	3,5-xyl	3,5-xyl	88	77
6	**18**	3,5-xyl	Ph	96	81
7	**19**	Ph	3,5-xyl	91	64
8	**20**	1-nap	1-nap	86	15
9	**21**	1-nap	Ph	93	64
10	**22**	Ph	1-nap	88	17
11	**23**	1-nap	2-nap	91	57
12	**24**	2-nap	1-nap	93	28
13	**25**	2-nap	2-nap	85	70
14	**26**	2-nap	Ph	91	73
15	**27**	Ph	2-nap	91	59
16	**28**	1-nap/Ph	1-nap/Ph	88	55
17	**29**	Ph/1-nap	Ph/1-nap	91	14
18	**30**	Ph/1-nap	1-nap/Ph	88	32
19	31	1-nap/Ph	Ph/1-Nap	68	30

[a] All ligands where synthesized and screened on the Synphase system from Mimotopes. Reactions were run between 0 °C and 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.

acids away from the metal had a negligible effect on the selectivity of the catalyst, while substitution of D-Val in the $i + 1$ position increased the selectivity slightly (88% ee).

Table 3



Ac-Www-Xps[a]-Xxx-Yyy-Pps[b]-Zzz-support

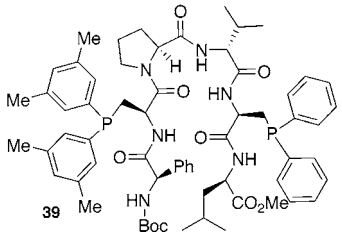
	compd	Www	Xxx	Yyy	Zzz	ee[e] (%)
1	**32**	D-Phg	Pro	D-Val	D-Leu	86
2	**33**	D-Phg	Oic	D-Ala	D-Leu	79
3	**34**	D-Ala	Pro	D-Ala	D-Phg	82
4	**35**	D-Phg	Pro	D-Ala	D-Ala	82
5	**36**	D-Phg	Pro	D-Ala	D-Phg	81
6	**37**	D-Ala	Pro	D-Ala	D-Ala	79
7	**38**	D-Phg	Pro	D-Tle	D-Leu	42
8	**18**	D-Phg	Pro	D-Ala	D-Leu	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 between 0 °C and rt using *N,O*-bis(trimethylsilyl)acetamide, TBAF, and dimethylmalonate. [d] Isolated yield. [e] Enantiomeric excess was determined by ^{1}H NMR analysis using [Eu(hfc)$_3$] shift reagent.

Following the optimization of the ligand system, the reaction conditions were examined. Upon examination of a number of solvents (DMF, THF, acetone, benzene, acetonitrile), acetonitrile was found to be the solvent that provided the highest selectivity with the polymer bound catalyst. At 0 °C in acetonitrile, ligand **32** 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 (**32**) was synthesized in solution and purified by chromatography (compound **39**). Reaction of peptide **39** in acetonitrile provided a catalyst that gave the addition product with comparable yield and selectivity to the reaction in acetonitrile when the catalyst is immobilized on the synthesis support (90% yield and 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 4, entry 6, 91% yield,

Table 4. Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe



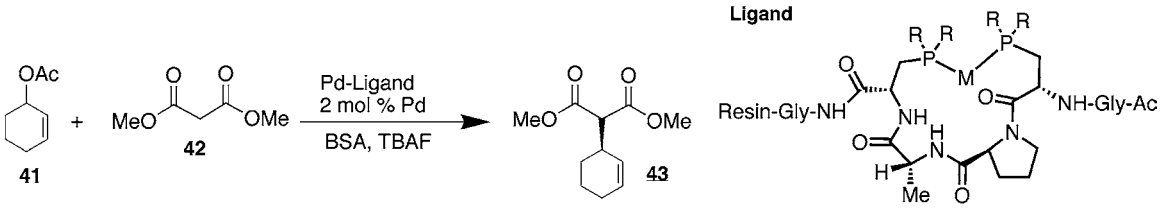
entry	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	0 to rt	82	88
2	toluene	0 to rt	89	89
3	acetone	0 to rt	91	88
4	CH_3CN	0 to rt	90	85
5	THF	0 to rt	92	90
6	**THF**	**0**	**91**	**95**
7	THF	−20	90	92
8	THF	−30	85	89
9	DMF	−45	92	85

[a] All reactions were run using *N,O*-bis(trimethylsilyl)acetamide, TBAF, and dimethylmalonate. [b] Isolated yield. [c] Enantiomeric excess was determined by ^{1}H NMR using [Eu(hfc)$_3$] shift reagent.

95% ee). *This selectivity is comparable to that of the best ligands known for this reaction.*[16−22]

(16) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905−7920.
(17) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
(18) Trost, B. M.; Bunt, R. C. *Angew. Chem, Int. Ed. Engl.* **1996**, *35*, 99−102.
(19) Trost, B. M. In *Catalytic Asymmetric Synthesis*; Ojima, T., Ed.; Wiley-VCH: New York, 2000; p 593.
(20) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919−2920.

Scheme 3



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

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

When the best ligand for 3-acetoxycyclopentene, Boc-D-Phg-Xps-Pro-D-Val-Pps-D-Leu-OMe, was used with the 3-acetoxycyclohexene, 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 (**40**) as the best ligand for this system (83% ee on support and 88% ee in solution, Scheme 3).

Reaction of acyclic allyl acetates resulted in low selectivities. Examination of models suggests that the palladium peptide complex may not be able to accommodate the extended allyl system obtained upon oxidative addition of the allyl acetate. We are currently synthesizing and studying isolated palladium complexes in an attempt to better understand the origins of selectivity with this system.

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".[23] 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. This paper, along with our previous paper,[8] 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. On the other hand, in the case of desymmetrization of meso diols, such a secondary structure provided poor selectivity. The example in Scheme 3 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 synthesized 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.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047−3050.
(22) Gilbertson, S. R.; Xie, D. *Angew. Chem.* **1999**, *38*, 2750−2752.
(23) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, *22*, 1445−1446.