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Coordination mode for turn-based phosphine ligands: the origin of selectivity in Pd catalysis

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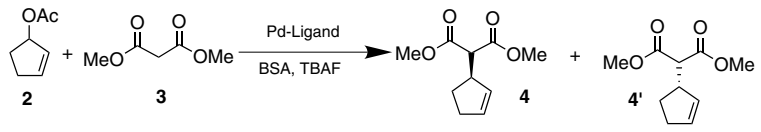
Abstract—A series of experiments was performed to determine the nature of the catalyst in peptide-derived phosphine ligands. The selectivity of the catalyst system was determined with four ligands that are diastereomeric at the phosphine containing amino acid. Additionally, a series of monophosphine ligands was synthesized and screened to determine if the active catalysts are derived from a phosphine–amide complex.

Serial phosphine containing amino acids have been developed that allow the incorporation of phosphine ligands into nearly any peptide structural motif.[1–4] Catalysis has been performed with rhodium and palladium phosphine complexes possessing helical and turn secondary structures, as well as in small non-structured peptides.[1,5–7] In the case of the palladium catalyzed alkylation of cyclopentenyl acetate with dimethylmalonate, we have found β-turn-based ligands that will perform the reaction in greater than 95% ee.[1] All of the peptide sequences we have examined have a number of amides that can potentially act as ligands for a transition metal. In our original design of a peptide-based ligand system, phosphines were chosen as the transition metal chelating group because it was felt that they would bind transition metals without interference from these amides. That said, there are a number of monophosphine–amide systems that have been successfully used in asymmetric catalysis.[8–13] While we have found that the thermodynamically stable structure has both phosphines coordinated to the metal, this in itself is not proof that an amide bound complex does not play a role as an active catalytic species. In this letter we report a series of experiments designed to investigate the origin of the observed asymmetric induction and to determine if the catalyst responsible for the observed selectivity is actually a bis-phosphine.

Determining the role of the chirality of the two individual phosphine containing amino acids (Pps) should provide information about the nature of the complex responsible for the selectivity observed during catalysis. In an attempt to separate the role of peptide secondary structure from the local chirality at Pps a peptide was synthesized with racemic phosphine amino acid. This provided a mixture of four peptides that are diastereomeric at the Pps chiral center, (*i* and *i*+3 positions) L/L, D/L, L/D, D/D. Coordination of palladium and catalysis of the alkylation of cyclopentenyl acetate (Scheme 1) provided selectivity of 55% ee (Table 1). Given that



Scheme 1.

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Table 1. Catalysis with diastereomeric peptide phosphine ligands

	i	*i*+3	Conversion (%)	ee (%)
1	D/L-Pps	D/L-Pps	>95	55
5	L-Pps	L-Pps	>95	74
6	D-Pps	L-Pps	>95	39
7	L-Pps	D-Pps	>95	73
8	D-Pps	D-Pps	>95	37

(1) Reactions were run with 4 mol% catalyst (1/4; Pd to ligand ratio) at rt in CH_3CN solvent, using *N*,*O*-bis(trimethylsilyl)-acetamide, TBAF and dimethylmalonate. The reactions were run with the ligand attached to the support it was synthesized on SynPhase™ crowns from Mimotopes, Ltd.
(2) Enantiomeric excess was determined by ^1H NMR analysis using [Eu(hfc)$_3$] shift reagent.
Ac-D-Phg-Xxx-Pro-D-Val-Xxx-D-Leu-support.

racemic Pps was used in the synthesis of the ligand, the observed selectivity is either due to the peptide secondary structure that is, the optically pure amino acids, or from one of the four ligands but not the others. One explanation is that of the four complexes formed, the selective catalyst may be significantly more active than the other diastereomers. This is commonly referred to as a positive nonlinear effect.[14,15] Another possible explanation is that only one diastereomer has the proper conformation to coordinate the transition metal and that this complex is responsible for the product.

To probe these issues, a series of experiments were carried out. If the previous results are due to the most active catalyst being the most selective then changing metal to ligand ratio (Pd/L) should have no effect on the selectivity of the system. Conversely, if the observed selectivity was due to preferential coordination of palladium by one of the four diastereomeric peptides, then increasing the Pd/L ratio should decrease the selectivity of the system (Fig. 1).

The metal to ligand ratio (Pd/L) was varied over a range of 2/1 to 1/8. The highest selectivity was observed with equal amounts of palladium and Ac-D-Phg-D,L-Pps-Pro-D-Val-D,L-Pps-D-Leu-peptide **1** (Fig. 2). Although conversions were high in all cases, the selectivity decreased significantly when the palladium to ligand ratio dropped below 1/2. It is known that [Pd(allyl)Cl]$_2$ alone does not catalyze this reaction so Pd/L ratios greater than 1 had only a small effect on the selectivity of the reaction. If only one of the four ligands in the mixture was catalyzing the reaction then one would have expected the ratio of 1/4 to maintain the same selectivity as 1/2. As can be seen this is not the case. There is a significant drop in selectivity when the ratio of metal to ligand is reduced from 1/2 to 1/4. This result is difficult to

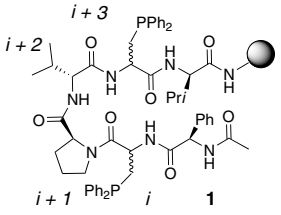

Figure 1.

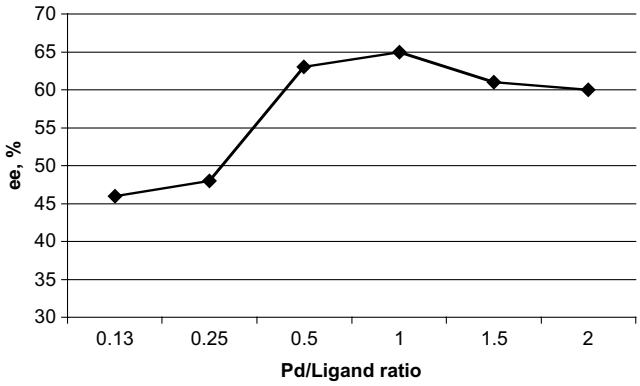

Figure 2.

explain on the bases of the more selective catalysts being more active. It can be rationalized if one considers that coordination of palladium to each of the four diastereomers may not occur equally. While we cannot rule out coordination of more than one ligand to a single palladium at low equivalents of metal having an effect on selectivity, this seems unlikely given that the ligands are immobilized on the solid support.

A second set of experiments were performed using each of the four possible diastereomers of the ligand separately. Each of these peptides was synthesized independently and then coordinated to palladium. This experiment allowed us to determine which of the four diastereomers was responsible for selective catalysis. The observed selectivities are shown in Table 1. All of the reactions proceeded to completion with two of them providing the product with good selectivity. Out of the four ligands, the two with L-Pps in the *i* position gave good selectivity (Table 1, 74% and 73% ee). While both peptides with D-Pps in the *i* position provided much lower selectivity (Table 1, 39% and 37% ee). One explanation for the data in Table 1 is that these ligands could be acting as monophosphines with the other coordination site on the transition metal being occupied by one of the amides in the peptide sequence. If ligands **5** and **7** coordinate the metal with the phosphine in the *i* position and then with an amide further down the chain, their gross structures many be very similar and consequently they may provide the product with the same selectivity. There are a number of reports in the literature of phosphine–amide ligands providing selectivity in the palladium catalyzed allylation reaction.[8–13] Additionally, we have reported previously an amino-acid-based ligand system that contained only one phosphine.[7]

If one assumes that the palladium complexes of the four pure ligands in Table 1 (**5**–**8**) have the same catalytic activity, than the selectivities of the four individual cases added together approximates the selectivity observed with the racemic ligand **1** (55% ee). This is evident that there is not one catalyst providing the product either through selective chelation or a nonlinear effect.

Throughout our work with turn-based ligands we have examined the complexes by ^{31}P NMR. In every case

Table 2. Catalysis with monophosphine peptide ligands

	i	*i*+3	Conversion (%)	ee (%)
9	L-Phe	L-Pps	>95	18
10	D-Phe	L-Pps	>95	4
11	L-Pps	D-Phe	>95	10
12	L-Pps	L-Phe	>95	13

(1) Reactions were run with 4 mol% catalyst at rt in CH_3CN solvent, using *N*,*O*-bis(trimethylsilyl)acetamide, TBAF and dimethylmalonate. The reactions were run with the ligand attached to the support it was synthesized on, SynPhase™ crowns from Mimotopes, Ltd.
(2) Enantiomeric excess was determined by ^1H NMR analysis using [Eu(hfc)$_3$] shift reagent.
Ac-D-Phg-Xxx-Pro-D-Val-Xxx-D-Leu.

we have found both phosphines to be coordinated to either palladium or rhodium, whichever transition metal we were working with at the time. While this illustrates that the most stable complex is the bisphosphine complex, it does not prove that there is not a species or intermediate present in small quantity that is responsible for the catalytic activity and selectivity. In the case of the ligands in Table 1 it is possible that a phosphine–amide complex could be responsible for the catalytic formation of the observed product. To determine if such a complex is involved in the formation of the observed product, we synthesized a series of monophosphines where one of L-Pps amino acids in ligand **5**, (Ac-D-Phg-L-Pps-Pro-D-Val-L-Pps-D-Leu) was replaced with D- or L-phenylalanine. The palladium complexes of each of these ligands catalyzed the reaction to complete conversion but in every case with very low selectivity (Table 2). These experiments support the hypothesis that it is a bisphosphine complex that is responsible for the products we observe in catalysis with our turn-based ligands.

Through a series of experiments we were able to determine that in our peptide-derived systems either the catalyst or catalyst precursor for the palladium catalyzed allylation reaction is a bisphosphine complex and that a phosphine–amide complex is probably not involved in the catalytic cycle. It appears that the selectivity in the reaction is principally due to the phosphine amino acid in the *i* position. In previous work we have found that the residues forming the turn are also vital.[6] Since the stereochemistry of the Pps in the *i*+3 position is not critical for selective catalysis, it is possible that peptide region near the Pps in the *i*+3 position is not structurally well organized. This information should be useful in the design of the next generation of catalysts.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.096.

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