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Kinetic Resolution in Palladium-Catalyzed Asymmetric Allylic Alkylations by a P,O Ligand System

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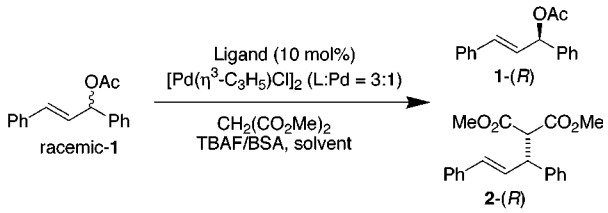
ABSTRACT



Through the investigation of peptide-based phosphine oxazoline ligands, a simple P,O ligand system was developed. This system provides palladium complexes that are capable of a very high degree of kinetic resolution of 1,3-diphenylprop-2-enyl acetate. The isolated palladium complex was synthesized, characterized, and determined to be an effective procatalyst.

Over the course of the past few years, we have been involved in the development of peptide-based phosphine ligands for asymmetric catalysis.[1−4] We have developed chemistry that allows for the introduction of phosphines into a variety of different peptide secondary structures. Additionally, we have used parallel synthesis in the construction of these new ligands.[5−8] Recently, a number of workers have become interested in the use of phosphine−oxazoline ligands in asymmetric catalysis.[9−22] In the course of screening a series of peptide-based phosphine−oxazoline ligands, we observed significant kinetic resolution of the starting material. This Letter reports the development of a simple P,O ligand system, the kinetic resolution of racemic starting allyl acetate, and attempts to discuss some of the mechanistic implications of our observations.

Initially we synthesized a series of phosphine−oxazoline ligands that were designed to have a β-turn secondary structure. These ligands were based on the observation that

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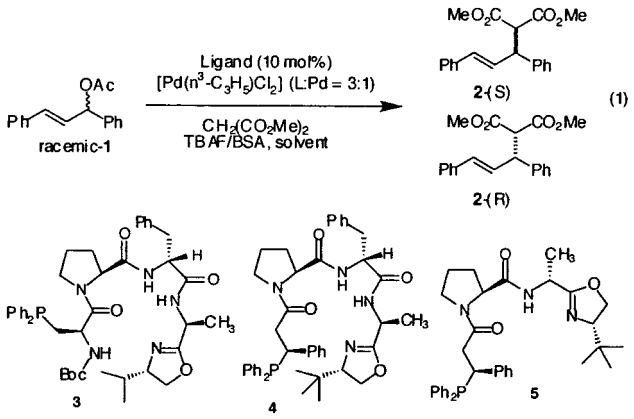
the proline D-amino acid sequence has a strong preference for the formation of β-turn type structures.[23−26] On one side of the presumed turn-forming residues, we positioned a phosphine-containing amino acid while on the other side we placed an oxazoline (**3**−**5**, Scheme 1). Our initial results with

Scheme 1

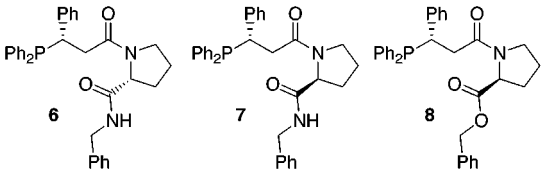


these ligands provided moderate selectivity, with ligand **5** providing a 40% ee.

In an attempt to develop more selective catalysts, we decided to study the chemistry of this system. There were a number issues that needed to be studied in order to improve the selectivity of this system. The first question we had to deal with was how the transition metal was chelated to the ligand. While these ligands were designed to be bidentate chelators, it was not a certainty that they were performing in such a manner. Additionally, if bidentate, we needed to determine that the palladium was bound to the phosphine and the oxazoline nitrogen. We fully expected that the phosphine would bind to the palladium, and this was verified by ^{31}P NMR. However, it was not clear that the oxazoline moiety would effectively compete with the amides in the peptide backbone. To test these issues, we synthesized a series of ligands that did not contain an oxazoline group (**6**−**8**, Table 1).

Surprisingly these ligands performed significantly better than the original design, with the palladium complex of ligand **7** providing the allylation product in up to 86% ee. Just as significant, a large difference in the rate of reaction for the two enantiomers of the starting material was observed. The *R* enantiomer of **1** reacted significantly faster than the *S* enantiomer. When the reaction run in THF was stopped at 51% conversion, the ratio of enantiomers of the starting material was 19/1 (S value of 42).[27−30] Through the years

Table 1. Catalysis of Reaction 1 with Ligands **6**−**8**



ligand	solvent	time	**1**(*S*):**1**(*R*)[a] (convn) S value[b]	ee of **2**, %[c]
6	toluene	3.5 h	1:1 (26%)	17 (*S*)
6	THF	4 h	1.4:1 (45%) 1.8	26 (*S*)
6	CH_3CN	4 h	1.4:1 (29%) 2.8	53 (*S*)
7	toluene	2 h	3.7:1 (52%) 5.6	64 (*S*)
7	THF	40 min	19:1 (51%) 42.0	86 (*S*)
7	CH_3CN	<5 min	1.3:1 (50%) 1.4	60 (*S*)
8	toluene	2 d	1.3:1 (25%) 2.6	44 (*S*)
8	THF	1 d	1:1 (11%)	12 (*S*)
8	CH_3CN	30 min	6.2:1 (57%) 7.0	52 (*S*)

[a] ee of recovered starting material was determined by HPLC on Chiralcel OJ; solvent *i*-PrOH/hexane = 1/99; flow rate 1 mL/min; retention time t_R(**1**-(*S*)) = 27.4 min, t_R(**1**-(*R*)) = 32.9 min. [b] $S = k_{fast}/k_{slow} = \ln[(1 - C/100)(1 - ee/100)]/\ln[1 - C/100)(1 + ee/100)]$ (C = conversion; ee = enantiomeric excess of the recovered substrate. [c] Enantiomeric excesses were determined by HPLC on Chiralpak AD; solvent *i*-PrOH/hexane = 10/90; flow rate 1 mL/min; retention time, t_R(**2**-(*R*)) = 10.0 min, t_R(**2**-(*S*)) = 13.7 min.

there have been reports of kinetic resolution in the palladium-catalyzed allylation.[31−34] To the best of our knowledge, the results we observe are among the highest S values observed for acyclic allyl acetates.[35]

Ligand **8** was synthesized to test the importance of the amide functionality. While catalysis with complexes of ligand **8** proceeded with some selectivity, the reaction rates were significantly slower than with **7**.

To help address the importance of the proline and the phenyl group α to the phosphine, ligands **9**, **10**, and **11** were synthesized and tested. In this case ligand **10** proved to give the highest selectivity, for both product formation as well as selectivity, between enantiomers of the starting material.

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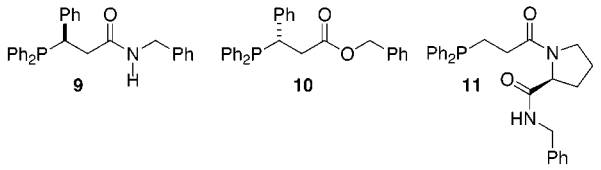
It is interesting that significant selectivity is observed with the very simple ligand **10**.[36] The results with ligand **11** give an indication of the importance of the phenyl group next to the phosphine. The only difference between ligands **7** and **11** is this phenyl group. In the case of **11**, the selectivity is low with no kinetic preference for either starting enantiomer. This appears to indicate that the principal element of control in this system is the chiral center next to the phosphine group.

On the basis of the observed selectivities in Table 2, it

Table 2. Catalysis of Reaction 1 with Ligands **9**−**11**[a]



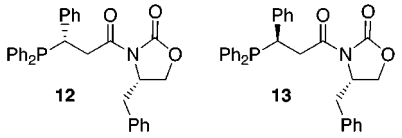
ligand	solvent	time	**1**(*S*):**1**(*R*)[b] (convn) S value[c]	ee of **2**, %[d]
9	toluene	4 h	1:1.6 (37%) 2.8	36 (*R*)
9	THF	1 d	1:5.5 (61%) 5.1	36 (*R*)
9	CH_3CN	7 h	1:2.3 (40%) 5.5	60 (*R*)
10	toluene	3.5 h	1.9:1 (38%) 4.1	72 (*S*)
10	THF	1.6 h	7.3:1 (58%) 7.6	64 (*S*)
10	CH_3CN	0.5 h	7.3:1 (64%) 5.4	61 (*S*)
11	toluene	10 min	1:1 (48%)	0
11	THF	<5 min	1:1 (60%)	8 (*S*)
11	CH_3CN	<5 min	1:1 (56%)	22 (*R*)

[a] All reactions were run at −25 °C. [b] ee of recovered starting material was determined by HPLC on Chiralcel OJ; solvent *i*-PrOH/hexane = 1/99; flow rate 1 mL/min; retention time t_R(**1**-(*S*)) = 27.4 min, t_R(**1**-(*R*)) = 32.9 min. [c] $S = k_{fast}/k_{slow} = \ln[(1 - C/100)(1 - ee/100)]/\ln[1 - C/100)(1 + ee/100)]$ (C = conversion; ee = enantiomeric excess of the recovered substrate. [d] Enantiomeric excesses were determined by HPLC on Chiralpak AD; solvent *i*-PrOH/hexane = 10/90; flow rate 1 mL/min; retention time, t_R(**2**-(*R*)) = 10.0 min, t_R(**2**-(*S*)) = 13.7 min.

appears that the preferred groups coordinating to the palladium are the phosphine and an amide or ester carbonyl. With this in mind, we decided to synthesize a set of ligands where the group next to the carbonyl ligand would be chiral as well as rigid. Ligands **12** and **13** were synthesized. Ligand **13** gave selectivity comparable to that of ligand **7**, with a very large difference in the rate of reaction between the two enantiomers of the starting material, when the reaction is run in toluene solvent (S value = 44).

In an effort to sort out the origin of the observed product selectivity and the difference in the rate of reaction between the two enantiomers of the starting material, the π-allyl complex of ligand **13** and palladium was synthesized and isolated (**15**). When this complex was employed as a procatalyst in THF, the extent of kinetic resolution and the ee of the product corresponded to the reaction catalyzed by the complex generated in situ from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and ligand **13** (Table 3). Only the *R* acetate was recovered at

Table 3. Catalysis of **1** with Ligands **12**−**13**



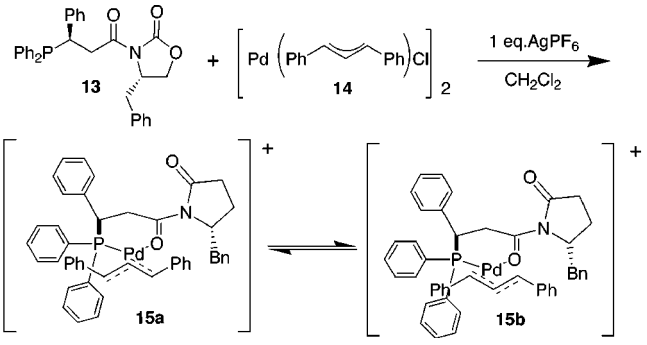
ligand	solvent	time	**1**(*S*):**1**(*R*)[a] (convn) S value[b]	ee of **2**, %[c]
12	toluene	1 h	2.4:1 (43%) 5.0	68 (*S*)
12	THF	3.5 h	3.8:1 (56%) 4.6	61 (*S*)
12	CH_3CN	5 min	1.5:1 (42%) 2.1	44 (*S*)
13	toluene	1 h	1:6.6 (45%) 44.0	88 (*R*)
13	THF	0.5 h	only (*R*) **1** (63%) 12	73 (*R*)
13	CH_3CN	<5 min	1:2.8 (56%) 3.3	62 (*R*)

[a] ee of recovered starting material was determined by HPLC on Chiralcel OJ; solvent *i*-PrOH/hexane = 1/99; flow rate 1 mL/min; retention time t_R(**1**-(*S*)) = 27.4 min, t_R(**1**-(*R*)) = 32.9 min. [b] $S = k_{fast}/k_{slow} = \ln[(1 - C/100)(1 - ee/100)]/\ln[1 - C/100)(1 + ee/100)]$ (C = conversion; ee = enantiomeric excess of the recovered substrate. [c] Enantiomeric excesses were determined by HPLC on Chiralpak AD; solvent *i*-PrOH/hexane = 10/90; flow rate 1 mL/min; retention time, t_R(**2**-(*R*)) = 10.0 min, t_R(**2**-(*S*)) = 13.7 min.

56% conversion, with the product obtained in 82% ee.

An NMR study of the complex indicates that the major conformation of the molecule is **15a** (Scheme 2). The ratio

Scheme 2



of isomers (**15a**:**15b**) as judged by ^{31}P NMR is 3.9:1 at room temperature. The NMR data support a P,O complex in which the phosphine and a carbonyl oxygen are coordinated to the palladium. This is significant since prior ligands of this type have been used in a 4-fold excess relative to the metal and have been proposed to be monodentate ligands.[37]

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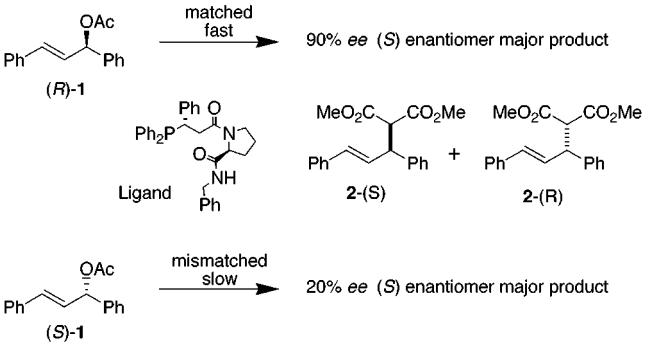
Stoichiometric addition of dimethylmalonate in THF gives the product that is expected from addition *trans* to the phosphine in complex **15a**. However, this addition proceeded with significantly lower selectivity than the catalytic reaction, 32% ee vs 82% ee.

The observed results are difficult to explain by a single mechanism. One theory would be that addition of the nucleophile is fast relative to the formation of the allyl complex. If this is so, then the ratio of the products is partially explained by the difference in rates of the formation of the two different allyl complexes. Thus, the difference in selectivity between the catalytic reaction and the stoichiometric addition of a nucleophile to an allyl complex would then be explained as the difference between adding to the kinetic ratio of allyl complexes vs the thermodynamic ratio. This explanation is complicated by the observation by Helmchen that in his system the isomerization of the allyl complex is 50 times faster than addition of the nucleophile.[17] In this reaction there have been observations of "memory effects". One way to describe such observations is that there are different ratios of rates between isomerization and nucleophilic attack. In most cases the situation Helmchen observed is operating. The allyl complex is undergoing isomerization significantly faster than nucleophilic addition. In select cases this does not appear to be the case. It is in these cases that the stereochemistry of the starting material has significant influence on the stereochemistry of the product.

Additionally, we have observed that when matched and mismatched sets of allyl acetate and ligand are reacted, the *S* enantiomer is obtained in both cases (Scheme 3). There appears to be a clear preference for formation of the *S* enantiomer regardless of the difference in the rate of reaction for the two enantiomeric allyl acetates. This is the type of preference that operates in any of the many successful asymmetric palladium-catalyzed allylations, given that it is possible to obtain good selectivity and high yields from racemic allyl acetates.

In the above discussion we assume that the nucleophile will add exclusively *trans* to the phosphine ligand. While this preference is well-known, it is not necessarily true that the addition is exclusively *trans* in P,O type ligands.

Scheme 3



A number of workers have attempted to discuss the origin of selectivity in this reaction. A variety of plausible explanations have been forwarded. It appears clear that the selectivity in this reaction is controlled by a balance of factors. Small changes in the ligand system or reaction conditions can not only decrease selectivity of the product but can also cause a different mechanistic pathway to be responsible for the selectivity that is observed. With the ligands reported here, we generally see good selectivity for one enantiomer of the product when we also have significant kinetic resolution. Clearly this is not necessary with other ligands given that in many cases the reaction using racemic substrate can be run to completion with excellent product selectivity.

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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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