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Asymmetric Allylic Alkylation Catalyzed by Palladium Complexes with New Chiral Ligands

Guoxin Zhu, Michael Terry, and Xumu Zhang*

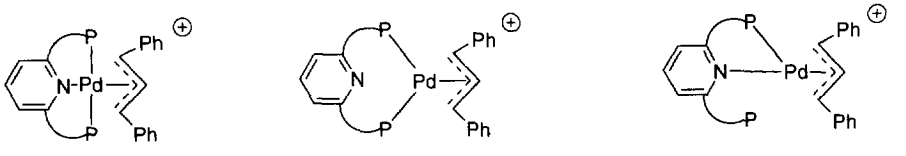
Department of Chemistry, 152 Davey Laboratory
The Pennsylvania State University
University Park, PA 16802

A potential chiral tridentate ligand based on 2,6-disubstituted pyridine has been prepared and its palladium complexes have been used in asymmetric allylic alkylation. Up to 75 % ee is achieved in the reaction between 1,3-diphenyl-2-propenyl acetate and dimethyl malonate. A control experiment with a similar ligand without pyridine suggests that the bidentate diphosphine coordination is responsible for the asymmetric reaction with this potential tridentate ligand. Copyright © 1996 Elsevier Science Ltd

Allylic alkylation catalyzed by Pd complexes is an extremely versatile carbon-carbon bond forming reaction.[1] Recently, asymmetric allylic alkylation has received considerable attention and excellent enantioselectivities have been documented in some cases with chiral bidentate phosphine, nitrogen and phosphine-nitrogen containing ligand systems.[2,3] In order to achieve substrate generality, the search for efficient ligand systems continues to receive attention. Unlike many asymmetric reactions in which the creation of stereogenic centers occurs within the coordination sphere of metal, metal catalyzed allylic alkylation generally involves bond-breaking and bond-forming steps away from the metal. A particularly intriguing idea proposed by Trost is to create a deep chiral pocket surrounding the substrate.[4] For chiral bidentate ligands, these pockets are generated by increasing the bite angle of the chelating phosphines. As the P-Pd-P bite angle increases, the diarylphosphine units are pushed towards the substrate and thus enhance chiral recognition. This idea has been successfully reduced to practice for efficient asymmetric allylic alkylations.[5]

We have recently synthesized several chiral tridentate ligands in our ongoing research on asymmetric catalysis.[6] Herein we report the results of a preliminary study on asymmetric allylic alkylation with a potential tridentate ligand containing a pyridine and two chiral phosphines. The possible π-allyl-palladium intermediates are shown in Scheme 1:

Scheme 1

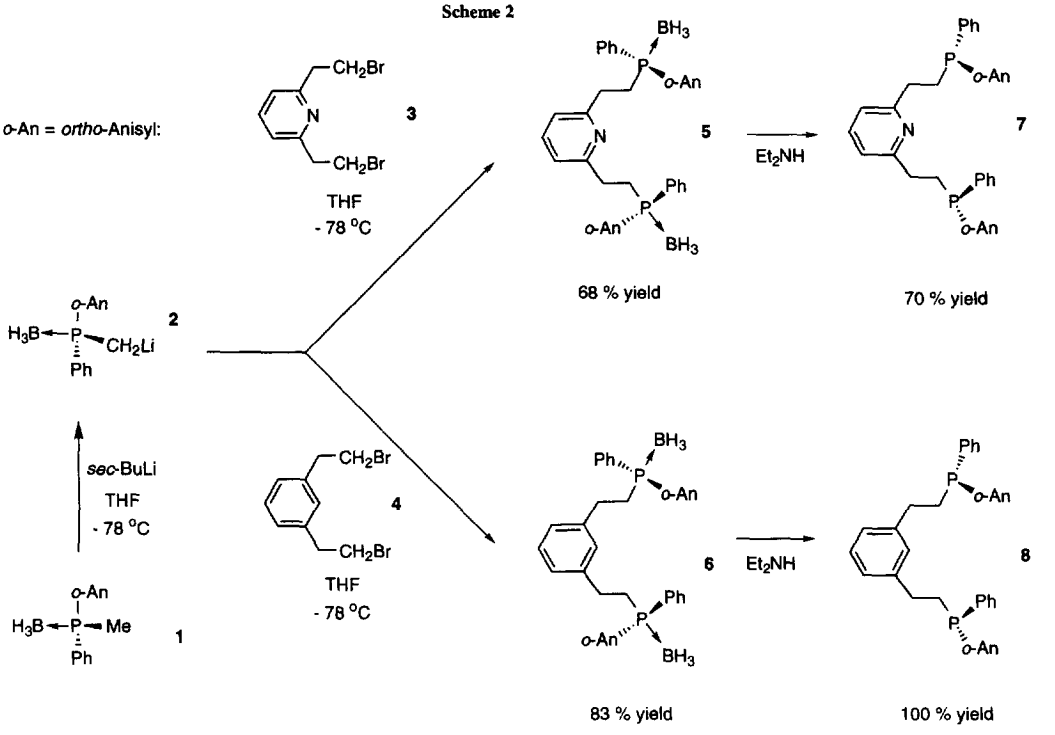


Tridentate ligands with two phosphines in the trans positions and a pyridine in the center could bind with a π–allyl-palladium to form an 18-electron species. Alternatively, 16-electron σ-allyl-palladium species with two phosphines or one pyridine and one phosphine are possible. Because there are only few potential chiral tridentate

ligands reported in the literature[6] and their coordination chemistry with transition metals was not very well studied in some cases, it is important to understand which coordination mode occurs in Scheme 1 for asymmetric allylic alkylation reaction. With the tridentate coordination mode or coordination with two phosphine atoms from the potential tridentate ligand, large P-Pd-P bite angles are expected which could induce high enantioselectivity for the asymmetric reaction.

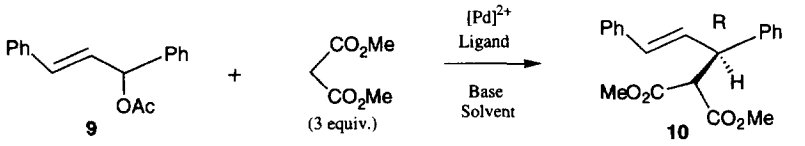
The synthesis of the chiral tridentate ligand **7** and bidentate ligand **8** used in this study is shown in Scheme 2.[7] The chiral bidentate ligand **8** differs from tridentate ligand **7** by substituting the pyridine ring with benzene. We can prepare optically pure chiral scalemic phosphine **1** on a gram scale according to a literature procedure.[8] Deprotonation of **1** with *sec*-BuLi *in situ* generates anion **2**, which reacts with 2,6-bis(bromomethyl)pyridine[9] **3** or the 2,6-bis(bromomethyl)benzene **4** to form **5** and **6**, respectively, in high yields. After removing the borane groups from **5** and **6**, tridentate ligand **7** and bidentate ligand **8** are obtained in pure form.

Scheme 2



The Pd-catalyzed asymmetric allylic alkylation reaction of substrate **9** was generally carried out using the following set of standard conditions:[3] catalyst formed *in situ* from 1 mol% of $[(\eta^3\text{–}C_3H_5)PdCl]_2$ and 2.2 mol% of a chiral ligand; a mixture of N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc (5%). Table 1 summarizes the results of these experiments. Racemic 1,3-diphenyl-2-propenyl acetate (**9**) reacts smoothly with dimethyl malonate generating optically active alkylation product **10** when chiral ligand **7** is employed. We have examined various bases in the asymmetric alkylation reaction (entry 1 with NaH, entry 5 with BSA, entry 2-4 and entry 6-9 with BSA-KOAc). Our results indicate that the combination of BSA and KOAc gives the best enantioselectivities in this reaction. The nature of the solvent also has some influence on the reaction enantioselectivity and rate. The reaction proceeds faster in THF (entry 1-2) and CH_2Cl_2 (entry 3-5) than in benzene (entry 6). However, the enantioselectivity is higher in benzene. Lowering the reaction temperature slows down the reaction but enhances the enantioselectivity. Up to 75 % ee has been obtained at -40 °C in toluene. Replacing ligand **7** with ligand **8**, both the enantioselectivity and the reaction rate are almost identical (entry 9).

Table 1. Palladium-catalyzed Asymmetric Allylic Alkylation



Entry[a]	Ligand	Base	Solvent	T (°C)	Time (h)	Yield (%)[c]	% ee[d]
1	**7**	NaH	THF	25	2.5	90	50
2	**7**	BSA-KOAc	THF	25	1.0	97	57
3	**7**	BSA-KOAc	CH_2Cl_2	25	1.5	93	61
4[b]	**7**	BSA-KOAc	CH_2Cl_2	25	1.5	93	57
5	**7**	BSA	CH_2Cl_2	25	1.0	93	55
6	**7**	BSA-KOAc	Benzene	25	4.5	99	66
7	**7**	BSA-KOAc	Toluene	-20	4.0	99	72
8	**7**	BSA-KOAc	Toluene	-40	35	97	75
9	**8**	BSA-KOAc	CH_2Cl_2	25	1.5	93	60

a. 1 mol% $[(\eta^3\text{-allyl})PdCl]_2$ and 2.2 mol% ligand; b. 2 mol% $Pd(OAc)_2$ and 2.2 mol% ligand; c. isolated yield; d.% ee was measured by HPLC using a Chiracel OD column; the R absolute configuration was determined by comparing the optical rotation with literature values (reference 3).

To probe the reaction mechanism, we have investigated catalytic precursor $\{[(\eta^3\text{–}C_3H_5)PdCl]_2$ + tridentate ligand **7**} by ^{31}P NMR. A clean singlet phosphine signal (+18.7 ppm) was observed, which is different from the free ligand **7** (-24.8 ppm). This result indicates that the two phosphine groups are in magnetically equivalent environments and they could both coordinated to the palladium metal (both tridentate P-N-P coordination and bidentate P-P coordination are acceptable at this condition). Alternatively, the ligand can undergo a fast exchange on the NMR time scale so the coordination with the pyridine nitrogen and one of the phosphines is possible. To understand what coordination geometry is responsible for the enantioselective alkylation, we synthesized the bidentate ligand **8** where the pyridine group in ligand **7** was replaced by a benzene ring. The experimental result (entry 9) shows that the enantioselectivity with ligand **8** is the same with ligand **7**. This strongly indicates the π-allyl-palladium with the potential tridentate ligand **7** prefers the coordination with two phosphine ligands to form a 16 elelctron species and pyridine does not coordinate to palladium in this intermediate.

In summary, we have achieved Pd-catalyzed asymmetric allylic alkylation with a potential tridentate ligand system containing two chiral phosphines and one pyridine. A control experiment with a corresponding ligand without pyridine indicates that the potential tridentate ligand may actually adopt a bidentate coordination in this asymmetric reaction. Continuing study will focus on reactions where tridentate ligands could be effective (e.g., Rh and Ru catalyzed asymmetric hydrosilylation reaction).

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7. Selected Data for compound **7**: ^{1}H NMR ($CDCl_3$) δ 7.6 – 6.8 (m, 27 H), 3.7 (s, 6H), 3.1 – 2.9 (br, m, 4H), 2.7 – 2.6 (br, m, 2H), 2.6 – 2.5 (br, m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.0 (s), δ 160.7 (d, J_{PC} = 20 Hz), 137.4 - 109.9, 55.0 (s), 34.3 (d, J_{PC} = 18.3 Hz), 25.8 (d, J_{PC} = 12.4 Hz); ^{31}P NMR ($CDCl_3$) δ –24.8 (s). compound **8**: ^{1}H NMR ($CDCl_3$) δ 7.6 – 6.8 (m, 22 H), 3.8 (s, 6H), 2.7–2.9 (br, m, 4H), 2.3 – 2.6 (ddt, J_{HH} =12.2, 5.4 Hz; J_{PH} = 58.0 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 161.0 (d, J_{PC} = 12.9 Hz), 142.9 (d, J_{PC} = 12.2 Hz), 137.5 - 110.2, 55.3 (s), 32.1 (d, J_{PC} = 19.4 Hz), 28.1 (d, J_{PC} = 11.1 Hz); ^{31}P NMR ($CDCl_3$) δ –24.9 (s).
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