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Asymmetric Allylic Alkylation Catalyzed by Palladium Complexes with a New Chiral Bisphosphine Ligand

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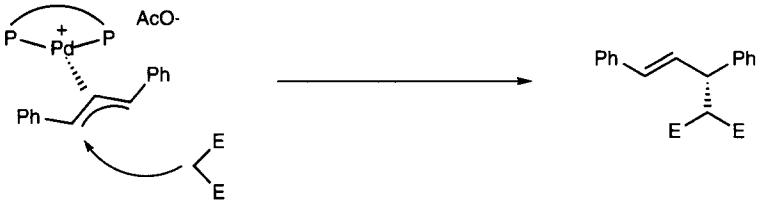
Abstract: A novel, chiral bisphosphine ligand has been synthesized and its palladium complexes have been used in asymmetric allylic alkylation. High reactivity and moderate selectivity have been realized in the reaction between 1,3-diphenyl-2-propenyl acetate and dimethyl malonate.

Transition metal catalyzed carbon-carbon bond forming reactions play an important role in organic synthesis. Stereochemical control in these reactions is of particular interest in the context of the synthesis of biologically active compounds.[1] For this reason, much work has been devoted to the design of chiral ligands to bring about a high degree of enantioselectivity. In particular, development of chiral phosphine ligands have played a significant role in asymmetric reactions promoted by transition metal complexes.[2] Herein we report the synthesis of a chiral bisphosphine ligand containing a large P-Pd-P bond angle and its application towards the allylic alkylation reaction.[3]

The mechanism of allylic alkylation involves bond making and bond breaking steps distant from the metal.[4] Nucleophilic attack occurs on the face of the allyl fragment opposite to the metal and therefore removed from the chiral environment imposed by the ligand (**Scheme 1**). As Trost has suggested, a larger P-Pd-P bond angle can create a deeper chiral pocket surrounding the substrate which may enhance chiral recognition.[5] Based on this idea, we have designed and synthesized a chiral bisphosphine ligand with a large P-Pd-P bond angle.

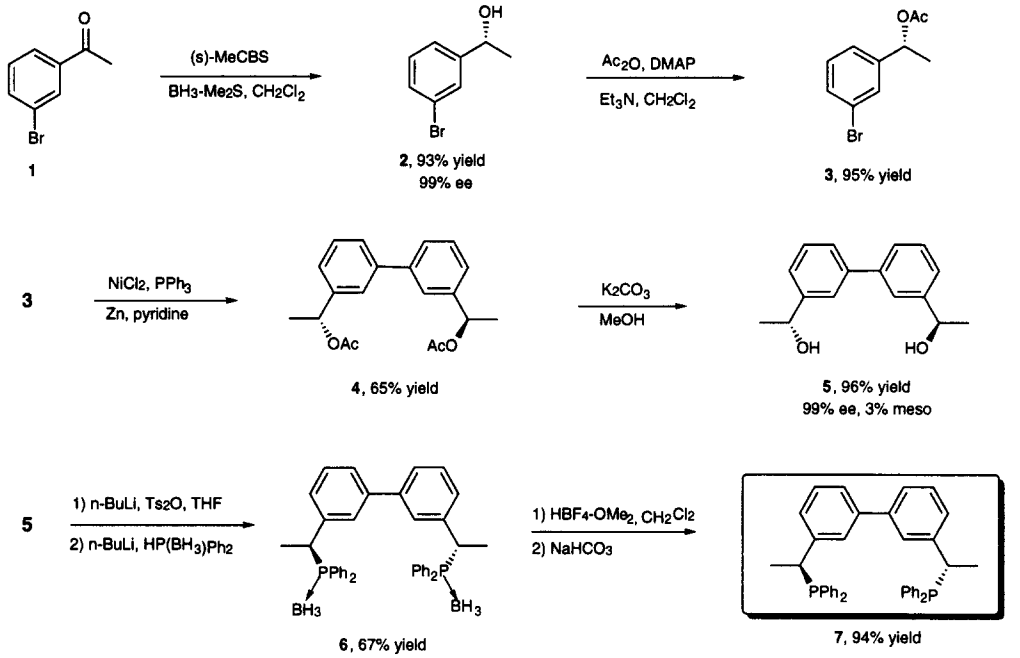
Scheme 1



The synthesis of phosphine ligand **7** is outlined in **Scheme 2**. The commercially available ketone **1** was reduced by $BH_3 \bullet Me_2S$ in the presence of a catalytic amount of (s)-MeCBS to give the chiral alcohol **2** in high enantiomeric excess.[6] The alcohol of **2** was then protected as its acetate in order to achieve a high yield of the coupled product **4**. Compound **4** can then be easily hydrolyzed to the desired diol **5** which upon HPLC analysis showed a ca. 3% meso impurity along with the desired C_2 compound with an enantiomeric excess of 99%.[7] Several unsuccessful attempts were made at removing the meso compound from **5** by recrystallization.

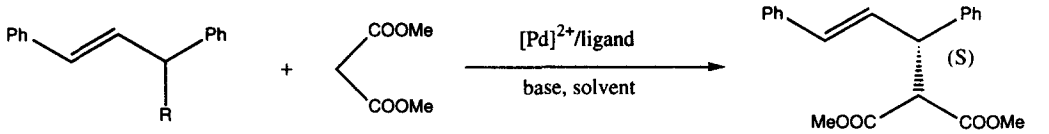
Phosphine **6** was then formed by *in situ* tosylation[8] of diol **5** followed by nucleophilic attack with the borane-protected diphenylphosphine anion. As with **5**, attempts at removing the meso compound from **6** by recrystallization proved futile. Finally the borane-protected phosphine **6** was converted cleanly to the desired free phosphine ligand **7**[9] in high yield by deprotection with strong acid.[10] Ligand **7** was then used in the asymmetric allylic alkylation reaction, the results of which are outlined in **Table 1**.

Scheme 2



The reaction of dimethymalonate with substrates **8a** and **8b** proceeded smoothly to form the optically active alkylation product **9**. An overall conclusion drawn from the results in **Table 1** is that enantioselectivities are not significantly affected by changes in the reaction conditions. The most noticeable changes are seen in the reaction rate and yield of product. We found that CH_2Cl_2 and CH_3CH_2CN gave the best results (entries 1, 5, 6, and 7), while the lowest enantioselectivity was observed in benzene (entry 6). Lowering the reaction temperature (entry 2) resulted in a marked decrease in yield while only slightly improving selectivity. The nature of the catalyst system was also studied (entries 3 and 4). It was found that changing the catalyst precursor to $Pd_2(dba)_3$ (entry 4) resulted in a high rate of reaction while having no effect on enantioselectivity. These same effects were also observed when the amount of catalyst was doubled (entry 3). Changing the substrate to the carbonate **8b** (entries 9 and 10) resulted in an enhanced reaction rate and yield, most notably at lower temperature (entry 10). Again the enantioselectivity was not significantly changed. Finally, using NaH as the base helped improve the yield in THF while having little effect on selectivity (entry 8).

Table 1. Palladium Catalyzed Asymmetric Allylic Alkylation



8a: R= -OC(O)Me
8b: R= -OCOOEt

9

Entry[a]	8	Base[g]	Solvent	T(°C)	Time(hr)	Yield(%)[c]	%ee[d]
1	**8a**	BSA-KOAc	CH_2Cl_2	25	2.0	92	50
2	**8a**	BSA-KOAc	CH_2Cl_2	0	24	54	57
3[b]	**8a**	BSA-KOAc	CH_2Cl_2	25	1.5	99	55
4[e]	**8a**	BSA-KOAc	CH_2Cl_2	25	1.5	97	53
5	**8a**	BSA-KOAc	CH_3CH_2CN	25	2.0	98	48
6	**8a**	BSA-KOAc	C_6H_6	25	48	66	41
7	**8a**	BSA-KOAc	THF	25	48	20	49
8	**8a**	NaH	THF	0	48	75	45
9	**8b**	BSA-KOAc	CH_2Cl_2	25	3	98	54
10	**8b**	BSA-KOAc	CH_2Cl_2	0	24	98	57
11[f]	**8a**	BSA-KOAc	CH_2Cl_2	25	12	99	59

a. 2 mol% $Pd(OAc)_2$ and 2.4 mol% ligand; b. 2 mol% $Pd(OAc)_2$ and 4.5 mol% ligand; c. isolated yield; d. %ee was measured by HPLC using a Chiracel OD column; the S absolute configuration was determined by comparing the optical rotation with literature values; e. 1 mol% $Pd_2(dba)_3$ was used; f. Diethyl acetamidomalonate was used as the nucleophile; g. BSA= *N,O*-Bis(trimethylsilyl)acetamide.

In conclusion we have reported the synthesis of a new chiral bisphosphine ligand and its application in the asymmetric allylic alkylation reaction. Conformational studies are currently under way to investigate the possibility that this ligand coordinates to metals in a trans manner.[11] We are also applying this ligand to various other asymmetric reactions.

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