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Enantioselective Palladium Catalyzed Allylic Alkylation with Phosphorus-containing C_2-symmetric Chiral Amine Ligands

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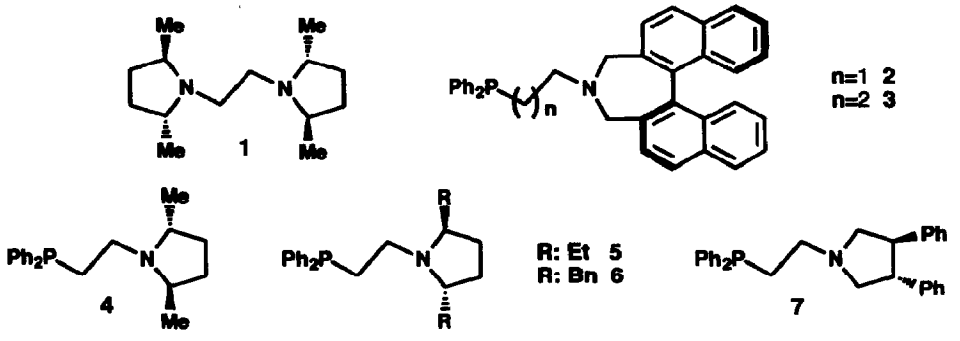
Abstract: In the presence of the palladium complex with the phosphorus-containing C_2-symmetric chiral amine ligand **2**, **3**, the asymmetric allylic substitution of racemic 1,3-diphenyl-2-propenyl acetate **8** with dimethyl malonate proceeded in high yield with remarkable enantiomeric excess.

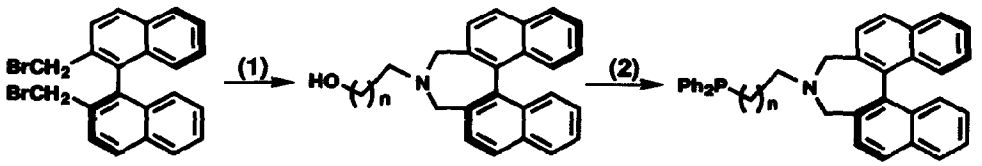
Enantioselective palladium catalyzed allylic alkylation has been exploited with a variety of chiral ligands.[1] Recently, chiral nitrogen ligands have received a great deal of attention.[2] Although the chiral nitrogen ligands possessing enantiomerically pure oxazolines have been studied energetically, there have been only a few reports on the optically active aliphatic tertiary amine.[2b,3] We reported in our previous paper that the palladium complex with a C_2-symmetric chiral diamine ligand **1** is effective for the enantioselective allylic substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.[3] Unfortunately, the diamine ligand lacks a high level of reactivity as it applies widely to the other nucleophiles and substrates. On the other hand, three research groups have reported promising results for asymmetric allylic alkylation by using phosphorus-containing chiral oxazoline ligands, which show enhanced reactivity.[4]

In this paper, we wish to describe the preparation of new phosphorus-containing C_2-symmetric chiral amine ligands (**2**-**7**) and their application to the enantioselective allylic substitution.



The syntheses of the chiral ligands **2** and **3** are described in Scheme 1. Optically pure (+)-2,2'-bisbromomethyl-1,1'-binaphthyl,[5a] which was derived from (+)-1,1'-binaphthyl-2,2'-dicarboxylic acid obtained by optical resolution,[5b] was cyclized to the homopiperidine derivatives by condensation with the corresponding amino alcohols.[6] Subsequent chlorination and phosphination with potassium diphenylphosphide in THF afforded ligand **2** or **3**[8] in about 70 % overall yield from (+)-2,2'-bisbromomethyl-1,1'-binaphthyl. Ligands **4-7** were also prepared from the corresponding chiral pyrrolidines[3] in four steps ((1) EtO_2CCOCl. (2) $LiAlH_4$. (3) $SOCl_2$, (4) Ph_2PH, tBuOK; 45-60% overall yield).

Scheme 1.



n=1 **2**
n=2 **3**

(1) $HO(CH_2)_nCH_2NH_2$:n=1,2, TEA, PhH, reflux.
(2) $SOCl_2$, dioxane; Ph_2PH, tBuOK, THF, reflux.

The corresponding allyl palladium complexes were generated in situ from 2.5 mol% of allylic palladium chloride dimer and the corresponding ligands **2-7** in dichloromethane under Ar atmosphere. Asymmetric allylic substitution was carried out by treatment of the allyl palladium complex and the 1 mmol of racemic 1,3-diphenyl-2-propenyl acetate **8** with 3 mmol dimethyl malonate in the presence of 3 mmol of N,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate.[9,10]

Some representative results are shown in Table 1. The reactions with the P/N ligands proceeded much faster than the reaction with the diamine ligand **1** to afford the allyl substituted product **9** in high yield.[3] Ligand **2** was found to be effective for the palladium catalyzed enantioselective allylic substitution. Interestingly, the enantiomeric excess depends significantly on the ratio of palladium to ligand. Treatment of the excess amount of palladium relative to the ligand **2** was necessary for the achievement of a high enantioselectivity level (entry 1, 2). In the presence of excess ligand relative to the palladium, the reaction was completed quickly (within 3 minutes) to afford a nearly racemic product (entry 3).[11] The chiral pyrrolidine ligands **4-7** proved to be less effective (entry 5-8). These results show that ligand **2**, which has chiral naphthyl rings in the axial orientation to the homopiperidine ring, would constitute a better chiral environment than the chiral pyrrolidine ligands with the pseudo-equatorial substituents.

Scheme 2.

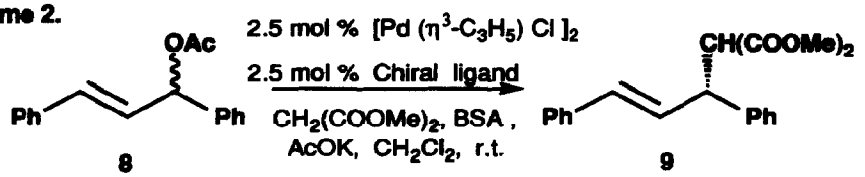


Table 1. Asymmetric allylic alkylation catalyzed by palladium complexes

Entry	Ligand/(mol%)	Time(min)	Yield(%)	%e.e.[a]	(Abs. config.)[b]
1	2/ 2.5	100	96	93	(R)
2	2/ 4.0	60	96	90	(R)
3	2/ 6.0	3	99	3	(S)
4	3/ 2.5	150	96	96[c]	(R)
5	4/ 2.5	90	94	20	(S)
6	5/ 2.5	140	96	19	(S)
7	6/ 2.5	150	95	11	(R)
8	7/ 2.5	160	93	39	(R)

a) The e.e. values were determined by HPLC with chiral column (Daicel Chiralpack AD, hex/ iPrOH=20/ 1).
b) The absolute configuration was determined by comparison of the rotation with literature values.[12]
c) $[\alpha]_D^{25}$ +19.8° (c 1.14, EtOH).

Further, we examined the ring size formed in the bidentate ligand-palladium complex to improve enantioselectivity. Trost has suggested that enlarging the ring should lead to closer contact of the chiral ligand to allyl termini and, consequently, to higher asymmetric induction.[9] The reaction with the palladium complex containing ligand **3**, which can form an expanded ring compared to that for ligand **2**, increased the enantioselectivity to 96%e.e. (entry 4).

The high asymmetric induction may be rationalized in terms of the steric and electronic effects in the intermediates.[1c,13] The reaction may proceed through the reactive intermediate **I** of the two diastereomeric intermediates under equilibration, and the nucleophile may attack the allylic terminus trans to the phosphine ligand, which is a better π-acceptor than the amine ligand (Figure 1). We are currently investigating the more detailed mechanism of this asymmetric allylic alkylation and extending our studies to other nucleophiles and substrates.

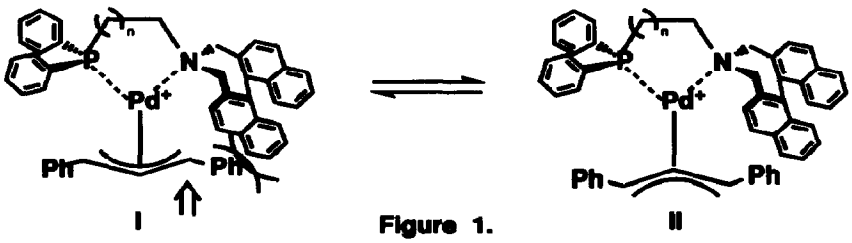


Figure 1.

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8. The ligand **2**: $[\alpha]_D^{25}$ -118°(c 0.92, CH_2Cl_2); ^1H NMR(270MHz, $CDCl_3$):δ 2.3-2.75 (m, 4H), 3.15 (d, 2H, J=12.2Hz), 3.69 (d, 2H, J=12.2Hz), 7.2-7.6 (m, 18H), 7.89 (d, 2H, J=8.3Hz), 7.92 (d, 2H, J=10.9Hz); ^{13}C NMR(67MHz, $CDCl_3$):δ 27.4 (d, J=12.2Hz), 51.7 (d, J=24.4Hz), 55.0, 125-140 (ArC).
   The ligand **3**: $[\alpha]_D^{25}$ -161°(c 0.55, CH_2Cl_2); ^1H NMR(270MHz, $CDCl_3$):δ 1.65-1.85 (m, 2H), 2.05-2.20 (m, 2H), 2.4-2.55 (m, 1H), 2.6-2.75 (m, 1H), 3.14 (d, 2H, J=12.2Hz), 3.63 (d, 2H, J=12.2Hz), 7.2-7.5 (m, 18H), 7.92 (d, 2H, J=8.3Hz), 7.94 (d, 2H, J=8.3Hz); ^{13}C NMR(67MHz, $CDCl_3$):δ 24.3 (d, J=17.1Hz), 25.8 (d, J=10.9Hz), 55.2, 56.3 (d, J=14.7Hz), 125-140 (ArC).
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13. During the course of revision of the present paper, a mechanistic study of the asymmetric allylic substitution catalyzed by the palladium complex with P/N ligand was reported; see: Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523.

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