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A phosphorus-containing chiral amidine ligand for asymmetric reactions: enantioselective Pd-catalyzed allylic alkylation †

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Abstract: Phosphorus-containing amidine **7** was prepared through several steps from L-valine **1**. The new ligand for asymmetric reactions was evaluated in the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate and pivalate **8a,b** with the nucleophile derived from dimethyl malonate as a preliminary study. Excellent levels of asymmetric induction up to 95% e.e. were achieved along with an efficient conversion.

Enantioselective allylic substitution reactions[1] focused on the use of phosphorus–nitrogen,[2] sulfur–nitrogen,[3] and phosphorus–sulfur[4] mixed donor bidentate ligands, have recently been demonstrated showing excellent levels of stereocontrol. Phosphorus–nitrogen ligands for the palladium-catalyzed allylic reactions, phosphorus-containing oxazoline ligands independently reported by several groups,[2a–e] cyclic amines,[2f,g] naphthylisoquinoline,[2h] and ferrocenylpyrazoles[2i,j] with the phosphino group, and other bidentate systems[2k,l] have been studied extensively. In this field, we are now developing new types of chiral ligands, phosphorus-containing amidines. The chelation by the more electron-rich imino nitrogen due to the amidine structure[5] and additional effects by the amino moiety such as stereocontrol would be expected in the present ligand. A variety of modifications such as exchange reactions to other amino groups[6] are possible in the amidine skeleton. It is expected that this flexibility is an advantage in the variation of reaction types and substrates. In the initial stage to evaluate the amidines as chiral ligands for asymmetric reaction, we wish to describe the use of phosphorus-containing amidine **7** for the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate and pivalate **8a,b** with the nucleophile derived from dimethyl malonate.

The chiral amidine ligand **7** is easily accessible from L-valine **1**, based on the procedure for (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphino)methylpyrrolidine (BPPM)[7] (Scheme 1). L-Valinol **2** prepared by the reduction of **1** was converted to (2*S*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-methyl-1-butanol **3** quantitatively by the protection reaction of the amino group with di-*tert*-butyl dicarbonate. (2*S*)-2-(*N*-*tert*-Butoxycarbonyl)amino-3-methyl-1-[(4-methylphenyl)sulfonyloxy]butane **4** was obtained from **3** using *p*-toluenesulfonyl chloride and pyridine. The phosphinylation of **4** with potassium diphenylphosphide was conducted in THF at −35°C, giving (2*S*)-2-(*N*-*tert*-butoxycarbonyl)amino-1-diphenylphosphinyl-3-methylbutane **5** in 96% yield which was converted into (2*S*)-2-amino-1-diphenylphosphinyl-3-methylbutane **6**[8] by the deprotection of the amino moiety using trifluoroacetic acid. (2*S*)-*N'*-[(1-Diphenylphosphinyl-3-methyl-2-butyl)]-*N*,*N*-dimethylformamidine **7**[9] was readily prepared by mixing **6** and *N*,*N*-dimethylformamide dimethylacetal.[10]

According to the Trost's procedure,[11] which is very often employed as a test allylic substitution reaction, the reactions of 1,3-diphenyl-2-propenyl acetate or pivalate **8a,b** with the nucleophile produced by reacting dimethylmalonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and lithium acetate as a catalyst were performed at room temperature in the presence of the palladium catalyst formed

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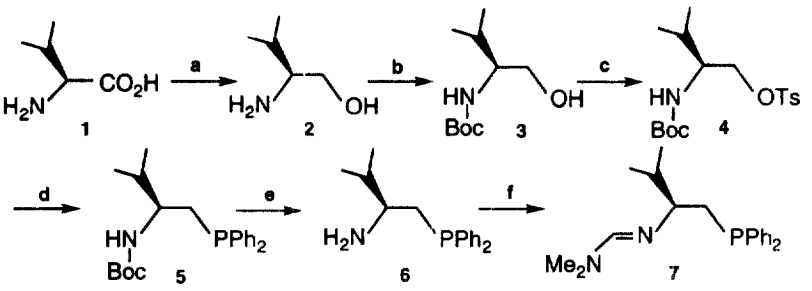
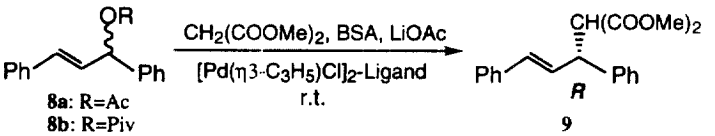


Reagents:(a) $LiAlH_4$, THF, reflux, 25 h, 91% (b) di-*tert*-butyl dicarbonate-Et_3N, CH_2Cl_2, r.t., 8 h, quant. (c) *p*-toluenesulfonyl chloride, pyridine, -35°C, 70% (d) Ph_2PK, THF, -35°C, 4 h, 96% (e) CF_3COOH, CH_2Cl_2, r.t., 12 h, 85% (f) $Me_2NCH(OMe)_2$, r.t., 3 h, quant.
Boc: *tert*-butoxycarbonyl, Ts: *p*-toluenesulfonyl

Scheme 1.

Table 1. Asymmetric allylic alkylation of *rac*-(*E*)-diphenyl-2-propenyl acetate and pivalate catalyzed by the palladium complex of amidine **7**[a]



8a: R=Ac
8b: R=Piv

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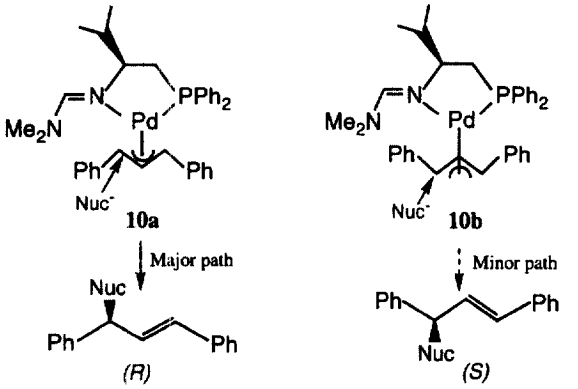
Entry	R	Molequiv. of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Solvent	Time (h)	Yield[b] (%)	E.e.[c] (%)
1	Ac	0.05	CH_2Cl_2	48	85	92(R)
2	Piv	0.05	CH_2Cl_2	24	99	93(R)
3	Piv	0.05	$ClCH_2CH_2Cl$	24	97	95(R)
4	Piv	0.05	THF	24	91	91(R)
5	Piv	0.025	CH_2Cl_2	24	87	94(R)
6	Piv	0.025	$ClCH_2CH_2Cl$	24	97	94(R)
7	Piv	0.01	$ClCH_2CH_2Cl$	24	90	93(R)[d]

a. Molar ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/1,3-diphenyl-2-propenyl acetate or pivalate/dimethyl malonate/BSA/lithium acetate=1-5/4-20/100/300/300/5.
b. Isolated yield by a preparative TLC on silica gel.
c. The enantiometric excess was determined by HPLC with a chiral column, Daicel Chiralpack AD (nHex:IPA=20:1)[2f]. The absolute configuration was confirmed by the optical rotation in addition to the comparison with HPLC peaks of the sample with *S* configuration[3c].
d. $[\alpha]_D^{30}$= +19.3 (*c* 0.8, EtOH)

from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the amidine ligand **7**. As summarized in Table 1, excellent levels of enantiometric excess up to 95% were obtained along with a quantitative conversion to methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate **9** in the present Pd–amidine catalyst system. The reduction of the amount of catalyst demonstrated that, essentially, there was no change at high level in the enantioselectivity. Significant solvent effect on the enantioselectivity was not observed.

It has been generally accepted as an enantioselecting step in the palladium-catalyzed allylations that nucleophilic attack to π–allyl complexes proceeds predominantly at the allyl terminus *trans* to a better π-acceptor which is the diphenylphosphinyl group in the current ligand (P–N of amidine).[2d,e,3a,c] In two diastereomeric allylpalladium complexes considered as π–allyl intermediates, it was demonstrated that the palladium-catalyzed allylations proceeded through the major diastereomer at equilibrium.[2d]

In the present reactions, the nucleophilic addition would proceed through the complex **10a** as a major path which led to the *R* configuration (Scheme 2). Some steric effect of the dimethylamino group to the π–allyl conformation may be related to the induction of a major path from **10a**, however the origin of asymmetric induction by the amidine ligand will be the subject of further discussion based upon future work.



Scheme 2.

In summary, we have developed the new type of chiral ligand, phosphorus-containing amidine, as a mixed donor bidentate ligand for the enantioselective allylic alkylations. Further investigations with respect to the extension to other asymmetric reactions and the modification of amidine ligand are currently in progress.

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