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Palladium-Catalyzed Asymmetric Allylic Amination Using Novel Types of Chiral Bisphosphine Ligands (BHMPs)[1]

Akira YAMAZAKI, and Kazuo ACHIWA*

School of Pharmaceutical Science, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

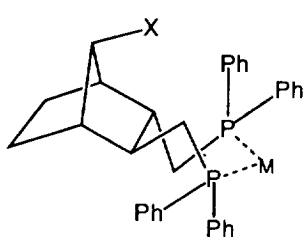
Abstract : New chiral bisphosphine ligands, which have a pendant side chain bearing a carboxylic acid at the terminal position, were designed and prepared. These new bisphosphine ligands were found to be efficient for palladium-catalyzed asymmetric allylic amination.

Asymmetric synthesis promoted by transition metal complexes is a very useful method. Until now, we have examined the function of each phosphino group of several bisphosphine ligands in catalytic asymmetric hydrogenations and clarified their electronic and steric effects on enhancing both the enantioselectivity and the reactivity of the catalyst.[2]

Next we focused our attention on design and synthesis of the chiral bisphosphine ligands bearing both the functionalized phosphines, which enhance their enantioselectivity and reactivity, and a functional side chain, which can interact with the substrate.[3] Recently this led us to synthesize a novel type of bisphosphine ligands bearing a hetero functional group.[4]

In this paper we describe the palladium-catalyzed asymmetric amination[5,6] of (*E*)-3-acetoxy-1,3-diphenyl-1-propene with benzylamine to show the effects of the functional side chain on stereoselectivity. Hayashi and Ito also applied the hydroxylated ferrocenyl phosphine ligands to the palladium-catalyzed asymmetric amination of ethyl 1,3-diphenyl-2-propenyl carbonate with benzylamine to give an amination product in 97%ee.[6] This high stereoselectivity was caused by interaction of the hydroxyl group on the ferrocenyl phosphine ligand with the incoming amine.

We designed and prepared a novel type of bisphosphine ligand (**1c-1f**) bearing a carboxyl group[7] on the side chain, expecting that the interaction of the carboxyl group on the ligand the incoming amine would direct it to attack selectively on one of the π-allyl carbon atoms.

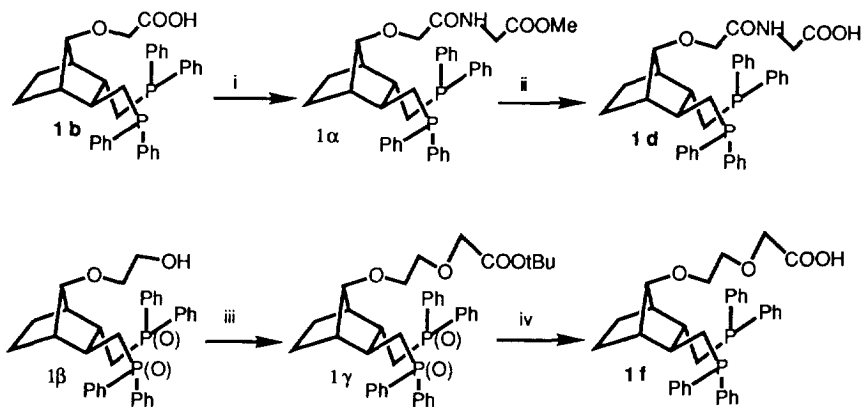


BHMP 7X (1)

BHMP	(**1a**) : X=H
BHMP-COOH	(**1b**) : X=OCH_2COOH
BHMP-Sar	(**1c**) : X=$OCH_2CON(CH_3)CH_2COOH$
BHMP-Gly	(**1d**) : X=$OCH_2CONHCH_2COOH$
BHMP-β-Ala	(**1e**) : X=$OCH_2CONH(CH_2)_2COOH$
BHMP-EA-COOH	(**1f**) : X=$OCH_2CH_2OCH_2COOH$

Preparations of the new ligands (**1c**, **1d**, **1e**, **1f**)[8] are described in Scheme 1. The chiral bisphosphine ligand bearing a amido-carboxylic acid (**1d**) was prepared from **1b**. Reaction of **1b** with glycine methylester in the presence of DEPC and diisopropylethylamine in DMF-CH_2Cl_2 at 0°C gave an amido ester (**1α**) in 83% yield. Hydrolysis of the methylester (**1α**) in the presence of LiOH in THF-H_2O (1/1) gave **1d** in 82% yield. **1c** and **1e** were similarly prepared from **1b**. The chiral bisphosphine ligand having an ethylene-ether unit (**1f**) was also prepared as follows. Etherification of the hydroxyl group of **1β** with *tert*-butyl bromoacetate gave an ether-linked *tert*-butylester-bisphosphinoxide (**1γ**) in 98% yield. Finally, reduction of the phosphinoxide (**1γ**) was achieved by refluxing with $HSiCl_3$-Et_3N in toluene under an atmosphere of argon and subsequent treatment with *p*-toluenesulfonic acid afforded **1f** in 39% yield.

Scheme 1.



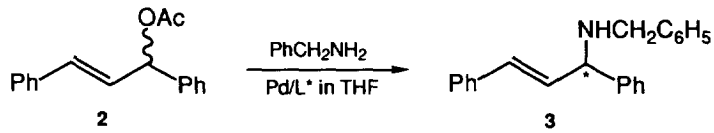
i .glycine methylester•HCl , DEPC , diisopropylethylamine , DMF-CH_2Cl_2 (1/1) , y.83%
ii . LiOH , THF-H_2O (1/1), y.82%
iii . NaH, $BrCH_2COO^tBu$, THF, y.98%
iv. 1). $HSiCl_3$, Et_3N, toluene, y.67% 2). *p*-toluenesulfonic acid, benzene, y.58%

The reaction of (*E*)-3-acetoxy-1,3-diphenyl-1-propene (**2**) with benzylamine was carried out in the presence of a palladium complex generated in situ by mixing a chiral ligand with $Pd_2(dba)_3$·$CHCl_3$ (P/Pd=2/1) as a catalyst. A solution of the chiral ligand (0.024 mmol) and tris(dibenzylideneacetone)dipalladium (0.01 mmol) in 5mL of THF was stirred at room temperature for 30 min. To this solution were added **2** (0.66 mmol) and benzylamine (0.80 mmol), and the mixture stirred at a given temperature for 17-42 h. The solvent was removed in vacuo, and the product N-((*E*)-1,3-diphenyl-2-propenyl)benzylamine (**3**) was isolated by preparative TLC on silicagel (toluene/AcOEt=20/1). The results are summarized in Table 1. The enantiomeric purity was determined by HPLC analysis of the benzamide derivative of **3** with a chiral column packed with Chiralcel OD-H (hexane/2-propanol=20/1).

On using BHMP (**1a**), which has no pendant side chain, **3** was obtained with low enantioselectivity in 56% yield (entry 1). However we could improve the enantioselectivity of (*R*)-**3**[6] up to 65.9%ee by introducing a carboxyl group at the terminal position of the pendant side chain (entry 6).

Table 1.

Asymmetric Allylic Amination of (*E*)-3-Acetoxy-1,3-diphenyl-1-propene (2) Catalyzed by Palladium Complexes of BHMP Derivatives[a]



entry	chiral ligand		reaction condition temp, °C	time, h	product (3) (yield %)[b]	%ee[c] (confign)[d]
1	BHMP	(1a)	25	42	56	9.4 (*R*)
2	BHMP-COOH	(1b)	21	28	95	13.4 (*S*)
3	BHMP-Sar	(1c)	21	30	72	17.7 (*S*)
4	BHMP-Gly	(1d)	21	17	41	55.4 (*R*)
5	BHMP-β-Ala	(1e)	40	40	69	64.9 (*R*)
6	BHMP-EA-COOH	(1f)	40	30	86	65.9 (*R*)

a. Reaction of 0.66 mmol of 2 with 0.80 mmol of benzylamine in 5 ml THF in the presence of 0.01 mmol of $Pd_2(dba)_3 \cdot CHCl_3$ and 0.024 mmol of a chiral ligand.

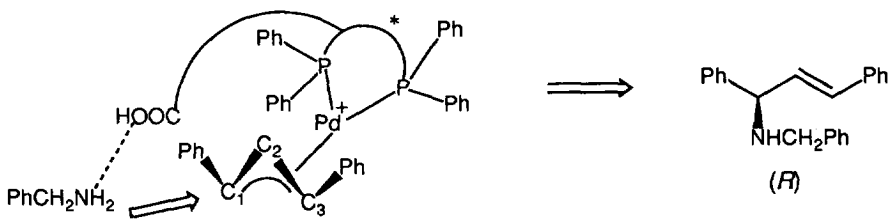
b. Isolated yield by preparative TLC on silica gel.

c. Enantiomeric excess was determined by HPLC analysis of the benzamide derivative, prepared by benzoylation of 3 with benzoyl chloride, pyridine, and DMAP in dichloromethane, with a chiral column packed with Chiralcel OD-H (hexane/2-propanol=20/1).

d. Determined by the sign of the specific rotation.[6]

On using **1d**, **1e**, **1f** (entries 4,5,6), it is probable that the carboxyl group located at the position close to the π-allyl carbon atom C_1 interacted with the incoming nucleophile and controlled the amine to attack selectively on the π-allyl C_1 carbon. Consequently, its (*R*)-enantiomer was produced in 66%ee (Figure).

Figure



Acknowledgement

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Reference and Notes

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8. **1c** : $[\alpha]_D^{26}$ -9.2 (*c* 0.52 C_6H_6) , **1d** : $[\alpha]_D^{23}$ -17.5 (*c* 1.18 THF) , **1e** : $[\alpha]_D^{23}$ -9.2 (*c* 0.49 C_6H_6) , **1f** : $[\alpha]_D^{26}$ -12.3 (*c* 1.07 C_6H_6).

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