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Asymmetric Synthesis of 2-Vinylmorpholine and 2-Vinylpiperazine Catalyzed by Palladium-BHMP Catalyst [1]

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Abstract: The reaction of 1,4-diacetoxy-*cis*-2-butene (**2**) with 2-(benzylamino)ethanol (**3a**) in THF in the presence of Et_3N and a catalytic amount of Pd(0)-BHMP-Gly (**1d**) gave optically active 4-benzyl-2-vinylmorpholine (**4a**) of up to 83.2%ee. Optically active 1,4-dibenzyl-2-vinylpiperazine (**4b**) (41.6%ee) was also obtained from 1,4-diacetoxy-*cis*-2-butene (**2**) and 1, 2-bis[(benzyl)amino]ethane (**3b**) in a similar manner. We could improve the enantioselectivity of (*R*)-**4a** and (*S*)-**4b** by introducing a carboxyl group at the terminal of the pendant side chain on the bisphosphine ligand.

Morpholine and piperazine derivatives have aroused increasing interest due to their presence in a large number of structures of therapeutic agents having important biological activities.[2] Most of the syntheses of optically active 2-substituted piperazine, such as piperazine-2-carboxylic acid have been carried out by resolution of diastereomeric menthyl N,N'-dibenzylpiperazine-2-carboxylates[3] and only one asymmetric synthesis of (*R*)-piperazine-2-carboxylic acid has been reported until now.[4]

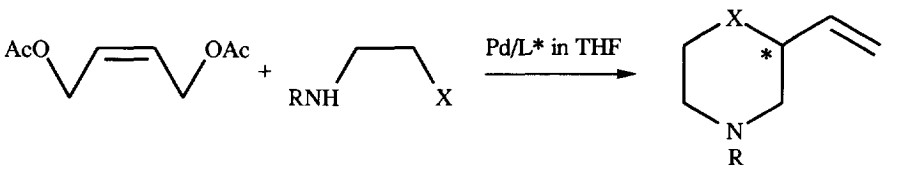
Asymmetric synthesis of heterocycles is difficult, so only a few methods have been reported to date.[5] Saegusa and co-workers reported that the construction of morpholine and piperazine skeletons by use of a palladium catalyst bearing a triisopropyl phosphine ligand.[6] Recently, Hayashi and Uozumi et.al. reported that the reaction of 1,4-diacetoxy-*cis*-2-butene with 2-(benzylamino)ethanol was catalyzed by a palladium complex coordinated with (*R*)-BINAP to give optically active (*R*)-4-benzyl-2-vinylmorpholine in up to 65% ee.[7] This asymmetric induction was controlled by the thermodynamic equilibration of the π-allylpalladium intermediate before the second nucleophilic attack giving the heterocycles. Similarly Sinou et.al. reported that the asymmetric synthesis of 2-vinyl-1,4-benzodioxane in the presence of a catalytic amount of a palladium(0) with BINAP.[8]

Recently we synthesized a novel type of bisphosphine ligands bearing a hetero functional group, and these ligands were found to be efficient for palladium-catalyzed asymmetric allylic alkylations[9] and aminations.[10] This asymmetric induction was caused by interaction of the heterofunctional group on the bisphosphine ligand with the incoming nucleophile.[11]

In this paper we examine the extension of this reaction to catalytic asymmetric cyclization by use of a chiral bisphosphine ligand bearing a heterofunctional group on the side chain, expecting that the interaction of

the carboxyl group on the BHMP ligands with the incoming nucleophile.

Scheme 1



2 **3** **4**

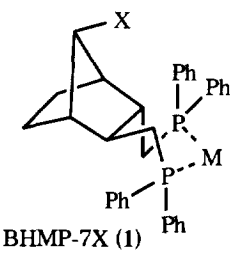
3a : R=$PhCH_2$, X=OH
3b : R=$PhCH_2$, X=$HNCH_2Ph$

4a : R=$PhCH_2$, X=O
4b : R=$PhCH_2$, X=NCH_2Ph

Table 1. Asymmetric Synthesis of 2-Vinylmorpholine and 2-Vinylpiperazine Catalyzed by Palladium-BHMP Catalyst.[a]

entry	Chiral Ligand		°C, hr	product, yield (%)[b]	ee%[c](confign)[d]
1	BHMP	**(1a)**	40, 72	**(4a)** 34	4.7 (2*R*)
2	BHMP-COOH	**(1b)**	45, 17	**(4a)** 59	32.4 (2*R*)
3	BHMP-Sar	**(1c)**	45, 15	**(4a)** 39	41.0 (2*R*)
4	BHMP-Gly	**(1d)**	45, 18	**(4a)** 54	83.2 (2*R*)[e]
5	BHMP-EA-COOH	**(1f)**	45, 24	**(4a)** 65	55.4 (2*R*)
6	BHMP-β-Ala	**(1e)**	40, 48	**(4a)** 49	66.3 (2*R*)
7	BHMP	**(1a)**	40, 66	**(4b)** 28	0
8	BHMP-COOH	**(1b)**	45, 46	**(4b)** 29	31.9 (2*S*)
9	BHMP-Sar	**(1c)**	40, 68	**(4b)** 57	26.7 (2*S*)
10	BHMP-Gly	**(1d)**	23, 18	**(4b)** 51	22.0 (2*S*)
11	BHMP-EA-COOH	**(1f)**	45, 46	**(4b)** 55	40.0 (2*S*)
12	BHMP-EA-COOH	**(1f)**	45, 17	**(4b)** 65	41.6 (2*S*)[f]
13	BHMP-β-Ala	**(1e)**	40, 65	**(4b)** 68	29.1 (2*S*)

[a] All entries were carried out under Ar in the presence of palladium complex prepared in situ by mixing a chiral ligand with $Pd_2(dba)_3$•$CHCl_3$(1/Pd=1) as catalyst. [b] Isolated yield after silica gel colum chromatography. [c] Determined by HPLC analysis with a stationary phase column (DAICEL CHIRALCEL-OJ). [d] Determined by the sign of the specific rotation.[7] [e] $[\alpha]_D^{22}$ +8.4 (*c* 0.54 chloroform). [f] $[\alpha]_D^{21}$ +47.0 (*c* 0.94 chloroform)



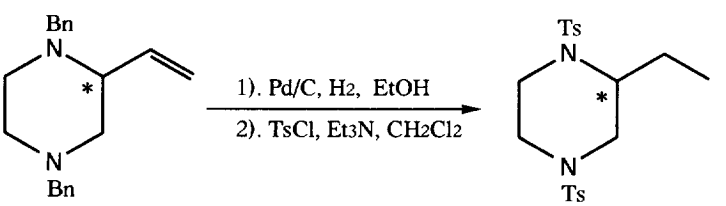
BHMP-7X (**1**)

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=$OCH_2CH_2OCH_2COOH$

Reaction of 1,4-diacetoxy-*cis*-2-butene (**2**) with 2-(benzylamino)ethanol (**3a**) was carried out in the presence of a palladium complex generated in situ by mixing a chiral ligand with $Pd_2(dba)_3$•$CHCl_3$ (**1**/Pd=1) as catalyst. Solution of a chiral ligand (BHMP-Gly (**1d**)) (0.013mmol) and Pd (0.013 mmol) in 2.5ml of THF was stirred at 21°C for 60 min. To the solution was added **3a** (0.25 mmol) and **2** (0.25 mmol), and the mixture was heated with stirring at 45°C for 18hr. After being cooled to room temperature, the solvent was removed in vacuo, and the product (*R*)-4-benzyl-2-vinylmorpholine (**4a**) (27mg 54%) was isolated by silica gel column chromatography. The enantiomeric excess was determined by HPLC analysis (CHIRALCEL OJ, n-hexane/2-propanol=100/1) to be 83.2% ee: $[\alpha]_D^{22}$ +8.4 (*c* 0.54, chloroform). The absolute configuration of 2-vinylmorpholine **4a** was determined to be (*R*) by the sign of the reported specific rotation.[7] Optically active 1,4-dibenzyl-2-vinylpiperazine (**4b**)[6] was also obtained from **2** and 1,2-bis[benzylamino]ethane (**3b**) in a similar manner. The results are summarized in Table 1.

The most stereoselective phosphine ligand was BHMP-Gly (**1d**) with e.e. up to 83.2% obtained in the formation of **4a** (entry 4). On using BHMP(**1a**), which has no pendant side chain, **4a** was obtained with low enantioselectivity in 34% yield (entry 1). In the case of forming **4b**, the most stereoselective phosphine ligand was BHMP-EA-COOH (**1f**) with e.e. up to 41.6% obtained (entry 12). Hayashi et.al. reported that on using (*R*)-BINAP, **4b** was obtained with low enantioselectivity (%ee<3) in 71% yield.[7] As shown in Table 1, the carboxylic group on the ligand have an important influence on the enantioselectivity of the cyclization. The absolute configuration of 1,4-dibenzyl-2-vinylpiperazine (+)-**4b** was determined by correlation with the known 1,4-bis(*p*-tolylsulfonyl)-2-ethylpiperazine (**5**).[7] Transformation of **4b** (30%ee) to **5** was carried out by hydrogenation (H_2 (1atm), 10%Pd-C in EtOH) and followed by N-tosylation (TsCl, Et_3N, in CH_2Cl_2) , which turned out to be the (*S*) isomer by measurement of the optical rotation ($[\alpha]_D^{22}$ +1.9 (*c* 0.95 $CHCl_3$)).

Scheme 2



4b **5**

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