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Asymmetric Cyclization of 3,4-Dihydro-2-Vinyl-2H-1,4-Benzoxazine Catalyzed by Palladium-BHMP Catalyst[1]

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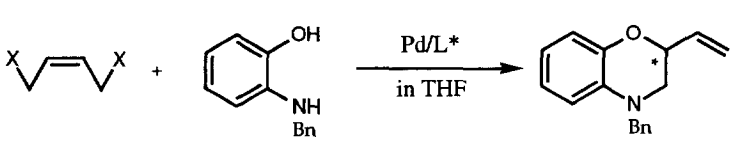
Abstract: The reaction of 1,4-diacetoxy-*cis*-2-butene **2a** with 2-(benzylamino)phenol **3** in THF in the presence of Et_3N and a catalytic amount of Pd(0)-BHMP-β-Ala **1c** gave optically active 4-benzyl-2-vinylbenzoxazine of up to 56.2%ee. The reaction of (Z)-2-butene-1,4-diylbis(methylcarbonate) **2b** instead of **2a** with 2-(benzylamino)phenol **3**, **4** was obtained with e.e. up to 71.4%. We could improve the enantioselectivity of (*R*)-**4** by introducing a carboxyl group at the terminal position of the pendant side chain on the bisphosphine ligand and by using a methyl carbonate ester **2b** instead of diacetate **2a**.

There are many therapeutically and biologically active compounds in the 3,4-dihydro-2H-1,4-benzoxazine series.[2] Catalytic asymmetric construction of heterocycles is difficult, so only a few methods have been reported to date.[3] Saegusa and co-workers reported the construction of morpholine and piperazine skeletons using a palladium catalyst bearing triisopropyl phosphite ligand.[4] Hayashi 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.[5] Similarly Sinou et.al. reported the asymmetric synthesis of 2-vinyl-1,4-benzodioxane in the presence of a catalytic amount of a palladium(0) with BINAP.[6]

In a previous paper, we showed the effectiveness of the catalytic cyclization of 2-vinylmolpholine using a palladium-BHMP catalyst, and improved the enantioselectivity of 2-vinylmorpholine up to 83.2%ee.[7] In this paper we examine the extension of this reaction to other heterocycles containing an aromatic ring by use of a chiral bisphosphine ligand bearing a heterofunctional group on the side chain, expecting that the heterofunctional group on the BHMP ligand would interact with the incoming nucleophile.

Scheme 1



2a : X=OAc
2b : X=OCO_2CH_3

3

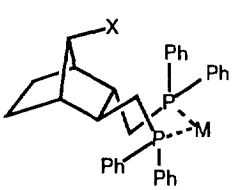
4

Reaction of (Z)-2-butene-1,4-diylbis(methylcarbonate) **2b** with 2-(benzylamino)phenol **3** was carried out in the presence of a palladium complex generated in situ by mixing a chiral ligand with $Pd_2(bda)_3$•$CHCl_3$ (**1**/Pd=1) as catalyst. Solutions of the chiral ligand (BHMP-β-Ala **1c**) (0.013mmol) and Pd (0.013mmol) in 2.0ml of THF was stirred at 20°C for 90 min. To the solution was added **2b** (0.25 mmol) and **3** (0.25 mmol), and the mixture was stirred at 20°C for 37hr. The solvent was removed in vacuo, the product (*R*)-4-benzyl-2-vinyl-benzoxazine **4** (31mg 48%) was isolated by silica gel column chromatography. The enantiomeric excess was determined by HPLC analysis (CHIRALCEL OB-H, n-hexane/2-propanol=300/1) to be 71.4%ee: $[\alpha]_D^{22}$ -11.6 (*c* 0.6 $CHCl_3$). The results are summarized in Table 1.

Table 1. **Asymmetric Cyclization of 3,4-Dihydro-2-Vinyl-2H-1,4-Benzoxazine Catalyzed by Palladium-BHMP Catalyst.**[a]

entry	chiral ligand	substrate	°C, h	yield (%)[b]	ee%[c](confign)[d]
1	(*S*)-BINAP	**2b**, -	20, 36	31	8.6 (2*R*)
2	(2*S*,3*S*)-NORPHOS	**2b**, -	20, 36	0	-
3	(*R*)-(*S*)-BPPFA	**2b**, -	20, 36	31	22.8 (2*S*)
4	BHMP (**1a**)	**2a**, Et_3N	45, 22	71	0
5	BHMP-Gly (**1b**)	**2a**, Et_3N	45, 44	32	27.5 (2*R*)
6	BHMP-Gly (**1b**)	**2b**, -	23, 18	71	50.4 (2*R*)
7	BHMP-Gly (**1b**)	**2b**, -	-20, 72	30	53.6 (2*R*)
8	BHMP-β-Ala (**1c**)	**2a**, Et_3N	40, 15	79	56.2 (2*R*) [e]
9	BHMP-β-Ala (**1c**)	**2b**, -	20, 37	48	71.4 (2*R*)
10	BHMP-Ad-PrOH (**1d**)	**2a**, Et_3N	45, 40	99	3.3 (2*R*)

[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 column chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (DAICEL CHIRALCEL-OB-H). [d] Determined by the sign of the specific rotation. [e] $[\alpha]_D^{22}$ -11.6 (*c* 0.61 $CHCl_3$).



BHMP 7X (1)

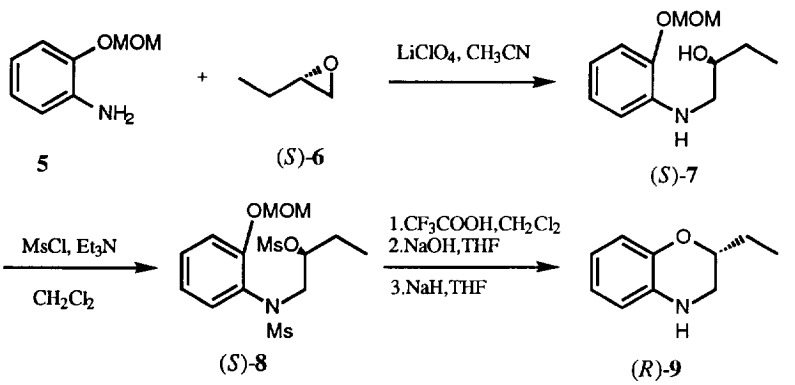
BHMP (**1a**) : X=H
BHMP-Gly (**1b**) : X=$OCH_2CONHCH_2COOH$
BHMP-β-Ala (**1c**) : X=$OCH_2CONH(CH_2)_2COOH$
BHMP-Ad-PrOH (**1d**) : X=$OCH_2CONH(CH_2)_3OH$

The most stereoselective phosphine ligand was BHMP-β-Ala **1c**. The use of methylcarbonate ester **2b**[8] instead of **2a** , was found to increase the enantioselectivity to 71.4% (entry 9), this trend was applied to the use of palladium-BHMP-Gly **1b** catalyst (entry 5, 6). Other heterofunctional groups on the bisphosphine ligand was examined. The use of BHMP-Ad-PrOH **1d** containing an alcohol unit at the terminal position of the pendant side chain that is about the same length of **1c**, gave **4** with low enantioselectivity (entry 10). Palladium complexes of other phosphine ligands including ((*S*)-(1,1'-binaphtalene)-2,2'-diylbis(diphenylphosphine)) (*S*)-BINAP[9], ((2*S*,3*S*)bicyclo[2,2,1]hept-5-ene-2,3-diylbis(diphenylphosphine)) (2*S*,3*S*)-NORPHOS[10], ((*R*)-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine) (*R*)-(*S*)-BPPFA[11] were

less stereoselective and/or showed no reaction (entry 1-3). As shown in Table 1, the carboxylic group on the ligand have an important influence on the enantioselectivity of the cyclization.

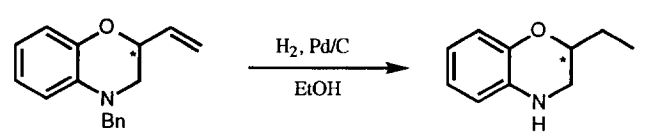
The absolute configuration of **4** was determined by correlation with (*R*)-**9** which was prepared from (*S*)-(-)-1,2-epoxybutane( ) by the following reactions: 2-methoxymethyloxy aniline **5** reacted with (*S*)-1,2-epoxybutane **6**[12] in the presence of $LiClO_4$ to give aminoalcohol (*S*)-**7**, the treatment of which with methanesulfonyl chloride in the presence of Et_3N gave (*S*)-**8**. Deprotection of the hydroxy group (*S*)-**8** with trifluoloacetic acid and followed by reaction with NaOH in THF solution and finally treatment with sodium hydride gave the cyclized product (*R*)-**9** as a pure material (Scheme 2).

Scheme 2



Comparison of the HPLC analysis (CHIRALCEL OD-H ; n-hexane/2-propanol=300/1) of (+)-**9** ($[\alpha]_D^{24}$ +22.3 (*c* 1.1 $CHCl_3$)) which was obtained from (-)-**4** ($[\alpha]_D^{23}$ -10.5 (*c* 1.0 $CHCl_3$)) by the palladium-catalyzed hydrogenation with that of authentic (*R*)-9 revealed the absolute configuration of (+)-**9** to be (*R*)-(+)-**9** (Scheme 3).

Scheme 3



(-)-**4** : $[\alpha]_D^{23}$ -10.5 (*c* 1.0 $CHCl_3$)

(+)-**9** : $[\alpha]_D^{24}$ +22.3 (*c* 1.1 $CHCl_3$)
53.8%ee:
(CHIRALCEL OD-H, n-hexane/2-propanol=300/1)

In conclusion, 3,4-dihydro-2-vinyl-2H-1,4-benzoxazine **4** was efficiently synthesized by a palladium catalyzed asymmetric cyclization. This functionalized benzoxazine is a potentially versatile intermediate for the synthesis of various biologically active compounds.

Acknowledgment

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