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SYNTHESIS AND APPLICATION OF CHIRAL BISPHOSPHINE LIGANDS CONTAINING A HETERO-FUNCTIONAL GROUP[1)]

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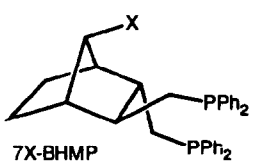
Abstract: New chiral bisphosphine ligands bearing hetero-functional groups were prepared by the use of asymmetric Diels-Alder reaction and silver-ion catalyzed rearrangement as key steps. The bisphosphines, especially bearing a carboxyl group, were found to be efficient ligands for palladium-catalyzed asymmetric allylic alkylation.

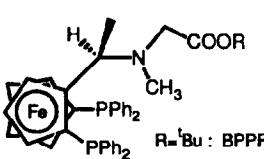
Asymmetric synthesis promoted by transition metal complexes is a very useful method in chiral synthesis. Previously we examined the function of each phosphino group of several bisphosphine ligands in the catalytic asymmetric hydrogenations and clarified their electronic and steric effects on enhancing both the enantioselectivity and the activity of the catalysts.[2)] On the other hand in order to improve the enantioselectivity, Hayashi and Ito et al. devised ferrocenyl bisphosphine ligands that have a side chain bearing a functional group at the terminal position.[3)] This functional group can interact with a substrate to improve the enantioselectivity. Recently Minami synthesized a novel type of chiral bisphosphine ligand bearing a carboxyl group, and applied it to asymmetric alkylation.[4)]

We report here the preparation and application of a novel type of bisphosphine ligands (**1b-f** and **2a, b**)[5)] containing a hetero-functional group which extends over the diphenylphosphine substituents.



7X-BHMP

X=H : BHMP (**1a**)
X=OCH_2OCH_3 : MOM-BHMP (**1b**)
X=OH : HO-BHMP (**1c**)
X=OCH_2CH_2OH : BHMP-CH_2OH (**1d**)
X=$OCH_2CO_2{}^tBu$: BHMP-$CO_2{}^tBu$ (**1e**)
X=OCH_2COOH : BHMP-COOH (**1f**)

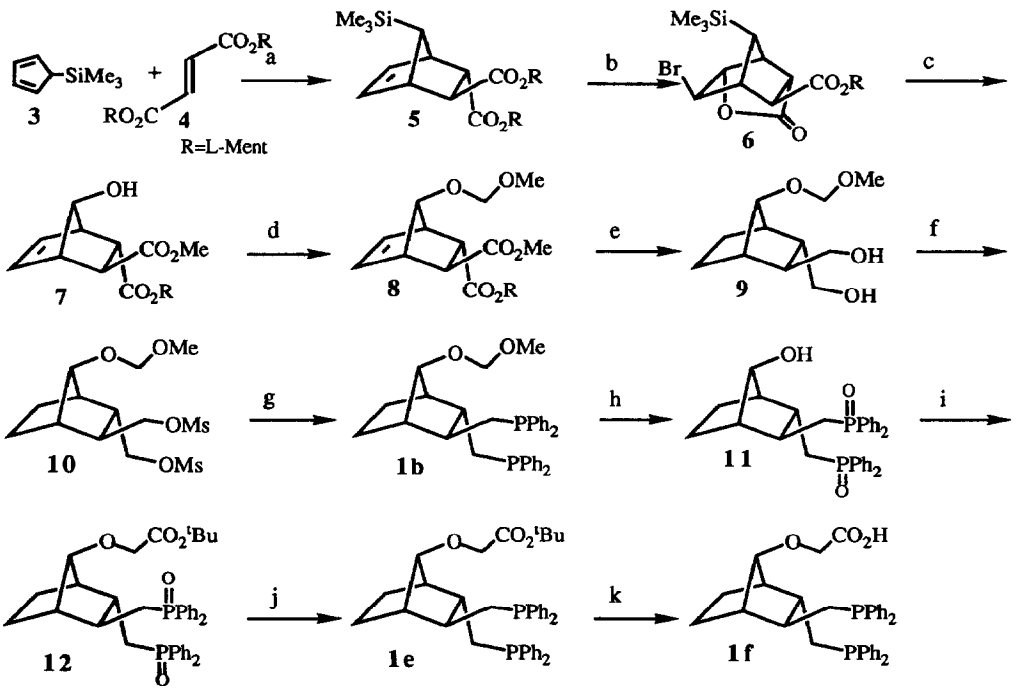


R=^{t}Bu : BPPF-$CO_2{}^tBu$ (**2a**)
R=H : BPPF-COOH (**2b**)

The synthetic route of the optically active bisphosphine ligands (**1b-f**) containing various hetero-functional groups on the side chain is shown in Scheme 1. Asymmetric Diels-Alder reaction of trimethylsilyl-cyclopentadiene (**3**) with dimenthyl fumarate (**4**) in toluene at -78°C gave norbornene dimenthyl ester (**5**) in a quantitative yield.[6)] Diastereomeric excess (97% d.e.) was determined by HPLC analysis of the ditosylate

derived via diol from **5** using a chiral column packed with Chiralcel OD (hexane/2-propanol=1/1). A single recrystallization from EtOH gave optically pure dimenthyl ester (**5**). Bromination of **5** gave bromolactone (**6**) (97%), which was allowed to rearrange by silver ion-catalyzed solvolysis in methanol.[7] The isolated alcohol (**7**) (88%) was protected with chloromethyl methyl ether to give **8** in a quantitative yield. Conversion of **8** to the corresponding diol with $LiAlH_4$, followed by reduction of the olefinic bond gave **9** (80%). The following mesylation of the diol (**9**) was carried out with mesyl chloride in pyridine to afford **10** (91%). Phosphination with sodium diphenylphosphide in DMF proceeded to give the bisphosphino compound (**1b**) (70%). Subsequent oxidation of **1b** with 10% H_2O_2 in CH_2Cl_2 afforded the corresponding bisphosphine oxide, and then cleavage of the methoxymethyl group with CF_3CO_2H gave hydroxy bisphosphine oxide (**11**) (90%). Etherification of **11** with *tert*-butyl bromoacetate gave **12** (78%). Reduction of the phosphine oxide (**12**) was achieved by heating with $HSiCl_3$-NEt_3 in toluene under an atomosphere of argon followed by treatment with 30% NaOH aq. to give bisphosphine *tert*-butyl ester (**1e**) (82%). Finally treatment of **1e** with *p*-toluenesulfonic acid afforded bisphosphine carboxylic acid (**1f**) (58%).

Scheme 1



a) Et_2AlCl, toluene, -78°C, 100%; b) Br_2, CH_2Cl_2, 97%; c) $AgNO_3$, MeOH, 88%; d) $ClCH_2OMe$, i-Pr_2EtN, CH_2Cl_2, 99%; e) 1) $LiAlH_4$, THF, 88%; 2) Pd/C, H_2, EtOH, 92%; f) MsCl, pyridine, 91%; g) $NaPPh_2$, DMF, 70%; h) 1) H_2O_2, CH_2Cl_2, 2) CF_3COOH, CH_2Cl_2, 90%; i) NaH, $BrCH_2CO_2{}^tBu$, THF, 78%; j) $HSiCl_3$, Et_3N, toluene, 82%; k) PTS,benzene, 58%.

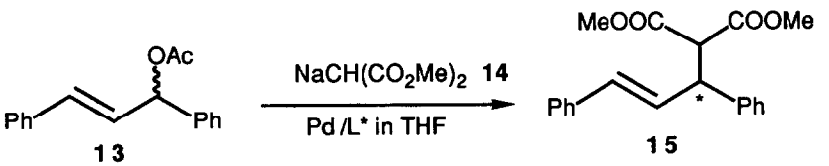


Table 1. Asymmetric Allylic Alkylation of (*E*)-3-Acetoxy-1,3-diphenyl-1-propene (**13**) Catalyzed by Palladium Complexes of BHMP, and Its Derivatives, and BPPF Analogs.[a]

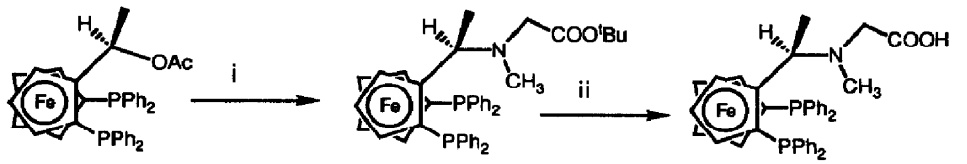
entry	chiral ligand		reaction condition temp,°C	time, h	product (% yield)[b]	% ee[c] (confign)	
1	BHMP	(**1a**)	40	75	77	0	
2	MOM-BHMP	(**1b**)	49	68	30	5.3	(*S*)
3	HO-BHMP	(**1c**)	40	68	36	6.4	(*R*)
4	BHMP-CH_2OH	(**1d**)	40	68	60	11.2	(*R*)
5	BHMP-CO_2tBu	(**1e**)	45	93	77	5.0	(*R*)
6	BHMP-COOH	(**1f**)	40	75	60	49.0[d]	(*R*)
7	BPPF-CO_2tBu	(**2a**)[e]	40	20	58	31.0[f]	(*S*)
8	BPPF-COOH	(**2b**)[e]	40	20	90	36.0[f]	(*S*)

[a]The chiral ligand (0.012 mmol), 3-acetoxy-1,3-diphenyl-1-propene (0.9mmol), and $Pd(OAc)_2$ (0.009 mmol) were dissolved in THF (5 ml). The mixture was added to a stirred suspension of sodium salt of dimethyl malonate prepared from sodium hydride (1.35 mmol) and the ester (1.35 mmol) in THF (5 ml) at room temperature, and the whole mixture was stirred at 40°C under argon. After usual work up, the product was isolated by preparative TLC on silica gel (toluene / ethyl acetate = 20 / 1). [b]Isolated yield. [c]Determined by HPLC analysis using a chiral column packed with Chiralcel OD-H (hexane/2-propanol=300/1). [d] $[\alpha]^{21}_D$ +8.6 (*c* 1.11 , EtOH). [e] $[Pd(\eta^3\text{–}C_3H_5)Cl]_2$ was used instead of $Pd(OAc)_2$. [f] $[\alpha]^{21}_D$ -6.6 (*c* 1.50 , EtOH).

The reaction of 3-acetoxy-1,3-diphenyl-1-propene (**13**) with the sodium salt of dimethyl malonate (**14**) was carried out in the presence of Pd complexes (0.01 eq.) of bisphosphines (**1a-f**) and BPPF-COOH (**2b**) . The results are summarized in Table 1. Enantiomeric excess was determined by HPLC analysis using a chiral column packed with Chiralcel OD-H (hexane/2-propanol=300/1). In the use of BHMP (**1a**), only racemic methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate (**15**) was obtained in 77% yield (entry 1). Palladium complexes of 7X-BHMP containing a hetero-functional group, especially a carboxyl group, were effective in producing **15** up to 49% ee ($[\alpha]^{21}_D$ +8.6 (*c* 1.11, EtOH))[8]. Thus we could improve the enantioselectivity of BHMP (**1a**) by introducing hetero-functional groups into the skeleton.

Since the carboxyl group was the most effective one, we designed and synthesized BPPF-COOH (**2b**), a ferrocenyl bisphosphine ligand bearing a carboxyl group (Scheme 2). (*R*)-(*S*)-BPPFOAc was allowed to react with sarcosine *tert*-butyl ester in MeOH under an argon atmosphere to give **2a**, which was treated with CF_3COOH affording **2b** in 64% over all yield. In the reaction using BPPF-COOH-Pd catalyst (entry 8), the enantiomeric excess was not so high as compared to that of entry 6, but improved to some extent as compared to the previously reported data ($[\alpha]^{20}_D$ -5.2, ethanol).[3] We are now in progress to modify the length of hetero-functional groups for application to various types of asymmetric reactions.

Scheme 2



(R)-(S)-BPPFOAc BPPF-$CO_2{}^tBu$ (2a) BPPF-COOH (2b)

i) sarcosine *tert*-butyl ester, MeOH, reflux, 5 h, 87%
ii) CF_3COOH, 74%

Acknowledgement

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References and Notes

1) Asymmetric Reaction Catalyzed by Chiral Metal Complexes. LVIII.
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4) Y. Okada, T. Minami, T. Yamamoto, and J. Ichikawa, *Chem. Lett.*, 547 (1992).
5) **1b**: $[\alpha]_D^{25}$ -3.6 (*c* 0.97, C_6H_6). **1c**: $[\alpha]_D^{20}$ -17.6 (*c* 0.98, C_6H_6), prepared by the reduction of the phosphine oxide **11**. **1d**: $[\alpha]_D^{21}$ -4.87 (*c* 1.73, C_6H_6), prepared by the reduction of the ester group and the phosphinyl groups of **12**. **1e**: $[\alpha]_D^{21}$ +3.0 (*c* 0.82, C_6H_6). **1f**: $[\alpha]_D^{22}$ -2.5 (*c* 0.98, C_6H_6). **2b**: $[\alpha]_D^{21}$ -245.5 (*c* 0.6, C_6H_6), mp 98-105°.
6) K. Furuta, K. Iwanaga, and H. Yamamoto, *Tetrahedron Lett.*, **27**, 4507 (1986).
7) I. Fleming and J. P. Michael, *J. Chem. Soc., Chem. Commun.*, 245 (1978).
8) The enantiomeric excess of **15** had been determined by ^1H NMR ($CDCl_3$) using a shift reagent [A. Toguni, *Tetrahedron: Asymmetry*, **2**, 683 (1991); J. Sprinz and G. Helmchen, *Tetrahedron Lett.*, **34**, 1769 (1993); C. G. Frost and J. M. Williams, *Tetrahedron Lett.*, **34**, 2015 (1993)] or by HPLC analysis of its diastereomeric amide derivatives [Y. Okada, T. Minami, Y. Umezu, S. Nishikawa, R. Mori, and Y. Nakayama, *Tetrahedoron; Asymmetry*, **2**, 667 (1991)]. We determined the enantiomeric excess by HPLC analysis, measured its optical rotations, and estimated the maximum optical rotation value of its pure (*R*)-enantiomer : $[\alpha]_D^{21}$ +17.6 (*c* 1.11 EtOH).