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New Monodentate Chiral Phosphine 2,6-Dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane(9-PBN): Application to Asymmetric Allylic Substitution Reaction

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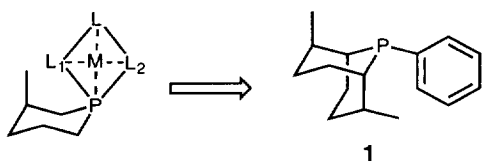
Abstracts: New monodentate chiral phosphines, (+)- and (-)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonanes ((+)- and (-)-9-PBNs), were prepared from 1,5-dimethyl-1,5-cyclooctadiene, and their application to the asymmetric allylic substitution reaction proved the utility of 9-PBNs as chiral phosphine ligands.

Catalytic asymmetric synthesis using transition metals coordinated with chiral auxiliaries is a powerful tool for obtaining optically active compounds in modern organic synthesis.[1] Optically active bidentate phosphines constituting a main class of chiral auxiliaries have been widely used in a variety of organic transformation with high stereoselection.[2] Recently, however, development of monodentate chiral phosphine ligands has gained increasing interest[3] for finding new catalytic transformations and improvement of bidentate phosphine mediated reactions, though the reactions using monodentate phosphine ligands disclosed to date have been mainly reported low or moderate stereoselection. We describe here the preparation and characterization of a new monodentate chiral phosphine without any other heteroatom and the successful application to the asymmetric allylic substitution reaction.

In contrast to the high stereoselection of rigid chelating bidentate ligands constructing an asymmetric environment, the low efficiency of monodentate phosphines seems to stem from the flexibility of coordination between the metal and the phosphine in the catalyst. In designing the monodentate phosphine bearing an inherent lack of chelating ability, we envisaged that the axial methyl group at the 3 position to the phosphorus atom on a 6-membered phosphorinane ring might serve for the construction of an asymmetric environment through the steric interaction between the methyl group and the other ligands (L_1 and L_2) (Scheme 1). Based on an easy preparation, the new phosphine **1** with the rigid structure was designed.

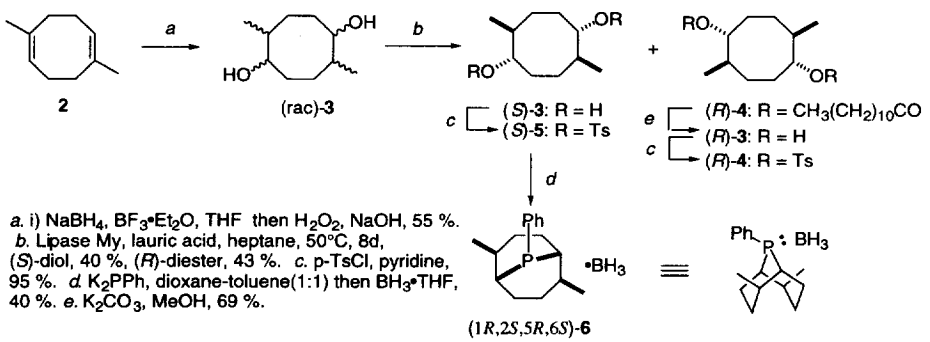


1

Scheme 1.

The synthesis of optically active **1** was efficiently carried out from commercially available 1,5-dimethyl-1,5-cyclooctadiene (**2**) through enzymatic resolution. First hydroboration of the diene **2** gave the (rac)-diol **3** with required stereochemistry in moderate yield. Subsequent resolution using lipase My[4] was found to be highly

effective for the (rac)-**3** in the presence of an excess of lauric acid in heptane, affording the (*S*)-**3** and (*R*)-dilauroyl ester **4** with high optical purity. Further purification of the optically pure of (*S*)-**3** was achieved by one recrystallization and the corresponding diMTPA ester of the (*S*)-**3** proved to be 100 %ee by NMR analysis. The (*R*)-**4** was hydrolyzed after recrystallization to afford the enantiomerically pure (*R*)-**3**. Absolute stereochemistry of each diol was confirmed by both results of the lipase My catalyzed esterification[4] and modified Mosher method.[5] Tosylation of (*S*)-**3** gave the labile ditosylate **5**. The double substitution reaction of freshly prepared **5** with dipotassium phenylphosphide in situ generated from phenylphosphine and the potassium-sodium alloy (75 : 25 weight %) proceeded to furnish after treatment with the borane-tetrahydrofuran complex the desired (1*R*,2*S*,5*R*,6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane borane complex **6**[6] ((-)-9-PBN•BH_3) as air-stable crystals. The stereochemical integrity of the final phosphine **6** and lack of racemization through the substitution reaction were unequivocally confirmed using chiral HPLC analysis.[7] The antipodal (+)-9-PBN•BH_3 was similarly prepared from the (*R*)-diol. The required free phosphine (-)-**1**[6] is quantitatively regenerated by reaction of the phosphine-borane with DABCO[8] and can be conveniently used as its hexane solution.

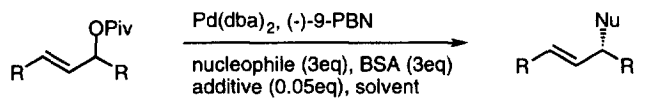


a. i) $NaBH_4$, BF_3•Et_2O, THF then H_2O_2, NaOH, 55 %. *b.* Lipase My, lauric acid, heptane, 50°C, 8d, (*S*)-diol, 40 %, (*R*)-diester, 43 %. *c.* p-TsCl, pyridine, 95 %. *d.* K_2PPh, dioxane-toluene(1:1) then BH_3•THF, 40 %. *e.* K_2CO_3, MeOH, 69 %.

As an application of our developed phosphine (-)-**1** in combination with a transition metal, we focused on the palladium-catalyzed asymmetric allylic substitution reaction of the allyl pivalate with malonic ester. Considerable efforts have been devoted to the asymmetric allylic substitution reaction and the most widely used bidentate ligands coordinated with palladium have achieved high stereoselection.[2,9,10] As shown in Table 1, the preliminary experiments using 1,3-diphenyl-2-propenyl pivalate and dimethyl malonate revealed that the enantiomeric excess of the product was strongly dependent on the nature of the additive (runs 3-5). The reaction with a small lithium in the additive resulted in excellent stereoselection. The typical π-allyl palladium chloride dimer often used for asymmetric allylic substitution reactions catalyzed the reaction with excellent stereoselection (run 1) but caused a lack of reproducibility and incomplete reaction for (-)-9-PBN. The optimum condition was obtained using the allyl pivalate **7a**, bis(benzylideneacetone)palladium ($Pd(dba)_2$), bis(trimethylsilyl)acetamide (BSA) as the base, lithium acetate, and 1,2-dichloroethane as the solvent (run 6). With 0.5 mol % $Pd(dba)_2$ and 1 mol % (-)-9-PBN using the above condition, the reaction was completed in 5 hr at room temperature under an argon atmosphere, affording the (*R*)-product **8a** in high yield with 94 %ee. Various active methylene

compounds can be used as nucleophiles, yielding the (*R*)-products with excellent stereoselectivity. In the case of (E)-1-methyl-2-butenyl pivalate (**7b**), the reaction sluggishly proceeded but gave the (*R*)-product **8g** with good stereoselectivity.

Table 1. Asymmetric Allylic Substitution Reaction using Palladium and (-)-9-PBN [a]



7 a: R = Ph
b: R = Me

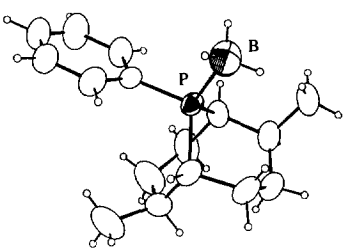
(R)-8

a: R = Ph, Nu = $CH(CO_2Me)_2$
b: R = Ph, Nu = $CH(COMe)_2$
c: R = Ph, Nu = $CH(CO_2t\text{-}Bu)_2$
d: R = Ph, Nu = $C(NHAc)(CO_2Et)_2$
e: R = Ph, Nu = $CH(COMe)(CO_2t\text{-}Bu)$
f: R = Ph, Nu = CH_2COMe
g: R = Ph, R = CH_3, Nu = $CH(CO_2Me)_2$.

run	R	Pd (mol %)	(-)-9-PBN (mol %)	nucleophile	additive	solvent	conditions	yield (%)	ee (%)
1	Ph	1[b]	1	$CH_2(CO_2Me)_2$	BTACl[c]	THF	4°C, 15h	35	95[d]
2	Ph	0.5[e]	1	$CH_2(CO_2Me)_2$	KOAc	CH_2Cl_2	rt, 24h	88	68
3	Ph	0.5	1	$CH_2(CO_2Me)_2$	CsOAc	CH_2Cl_2	rt, 24h	100	65
4	Ph	0.5	1	$CH_2(CO_2Me)_2$	KOAc	CH_2Cl_2	rt, 24h	88	76
5	Ph	0.5	1	$CH_2(CO_2Me)_2$	LiOAc	CH_2Cl_2	rt, 24h	100	88
6	Ph	0.5	1	$CH_2(CO_2Me)_2$	LiOAc	$(CH_2Cl)_2$	rt, 5h	100	94
7	Ph	1	2	$CH_2(COMe)_2$	LiOAc	$(CH_2Cl)_2$	40°C, 2d	100	96[f]
8	Ph	1	2	$CH_2(CO_2t\text{-}Bu)_2$	LiOAc	$(CH_2Cl)_2$	40°C, 3d	96	83[f]
9	Ph	2	4	$CH(NHAc)(CO_2Et)_2$	LiOAc	$(CH_2Cl)_2$	rt, 3d	100	94[f]
10	Ph	1	2	$CH_2(COMe)CO_2t\text{-}Bu$	LiOAc	$(CH_2Cl)_2$	rt, 3d	96	97[g,f]
11	Me	5	10	$CH_2(CO_2Me)_2$	LiOAc	$(CH_2Cl)_2$	rt, 3d	59	70[h]

a. The reaction was carried out using an allyl ester (1 mmol), a nucleophile (3 mmol), BSA (3 mmol), and an additive (0.05 mmol) in 1,2-dichloroethane (5 mL). *b*. $[(\pi\text{-}C_3H_5)PdCl]_2$ in place of $Pd(dba)_2$ was used. *c*. BTACl: benzyltriethylammonium chloride. 1.62 equivalent was used. *d*. HPLC analysis using Daicel Chiralcel OD. *e*. $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0025 mmol) in place of $Pd(dba)_2$ was used. *f*. HPLC analysis using Daicel Chiralpak AD. *g*. Determined after de-*tert*-butoxycarbonylation. *h*. GLC analysis using Chiraldex G-TA.

For elucidation of the structure of the catalyst affording high stereoselection, X-ray crystallographic analysis was carried out on the phosphine-borane complex (1*R*,2*S*,5*R*,6*S*)-**6**. Surprisingly, the molecular structure of **6** was found to occupy a chair-boat conformation in place of the chair-chair conformation (Scheme 2).[11] The ring with the axial phenyl group had a boat conformation and the phenyl one occupied a face-face conformation to the boat ring.



Scheme 2.

In summary, we succeeded in the development of the new monodentate phosphines, 9-PBNs, without any other heteroatom. The successful application to the asymmetric allylic substitution reaction proves the utility of 9-PBNs as an optically active phosphine ligand. We are now intensively working to explore the mechanism of

asymmetric induction with an exceptionally high level for monodentate phosphine ligands and the extension of asymmetric synthesis using 9-PBNs.

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6. (1*R*,2*S*,5*R*,6*S*)-**6**: mp 165-169°C; $[\alpha]^{29}_{D}$= +2.5 (c 1, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 0.81-0.99 (m, 1H), 0.95 (d, J=7.3 Hz, 3H), 1.50 (d, J=7.3 Hz, 3H), 1.55-2.77 (m, 10H), 7.43-7.60 (m, 5H); Anal. Calcd for $C_{16}H_{26}BP$: C, 73.87; H, 10.07. Found: C, 73.72; H, 9.95. (-)-(1*R*,2*S*,5*R*,6*S*)-**1**: $[\alpha]^{29}_{D}$= -30.7 (c 1, n-hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86-0.95(m, 1H), 0.88 (d, J=7.1 Hz, 3H), 1.27(m, 1H), 1.30 (d, J=7.3 Hz, 3H), 1.48(m, 1H), 1.6-2.38 (m, 8H), 2.49(d, J=10 Hz, 1H), 7.13(m, 1H), 7.24(m, 2H), 7.38(m, 2H).
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11. Crystal data for (1*R*,2*S*,5*R*,6*S*)-**6**: formula $P_1C_{16}B_1H_{26}$, F.W. 260.2, orthorhombic, space group $P2_12_12_1$, a = 7.760(2)Å, b = 12.415(2)Å, c = 16.231(2)Å, U = 1563.6(7)Å^3, Z = 4, R = 0.055, Rw = 0.071.

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