Synthesis of a Novel Type of Chiral Bisphosphine Ligand (NORPHOS-7-NEt_2) with an Amino Group for Neighboring Participation in Asymmetric Allylic Alkylation[1]

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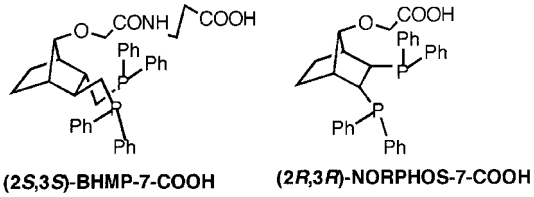
Abstract: A new chiral bisphosphine ligand, NORPHOS-7-NEt_2, with an amino group has been prepared. It has been applied to the Pd-catalyzed asymmetric allylic alkylation of *rac*-(*E*)-diphenyl-2-propenyl pivalate upon using (2*S*,3*S*,7*R*)-NORPHOS-7-NEt_2 (**1**) (**M**-Chirality) having an amino group on the ligand, the same absolute configuration product was obtained as compared to using (2*R*,3*R*)-NORPHOS (**P**-Chirality). This result clearly indicated the possibility of the interaction of the amino group on the ligand with the incoming nucleophile.

Recently we synthesized a novel type of chiral bisphosphine ligand BHMP-7-X[2] and NORPHOS-7-X[3] with a carboxyl group which was found to be efficient for palladium-catalyzed asymmetric allylic alkylation,[2] amination,[4] cyclization[5] and asymmetric hydrogenation[3] by interaction of a carboxyl group on the phosphine ligand with the incoming nucleophile and the substrate.[6]



(2*S*,3*S*)-BHMP-7-COOH **(2*R*,3*R*)-NORPHOS-7-COOH**

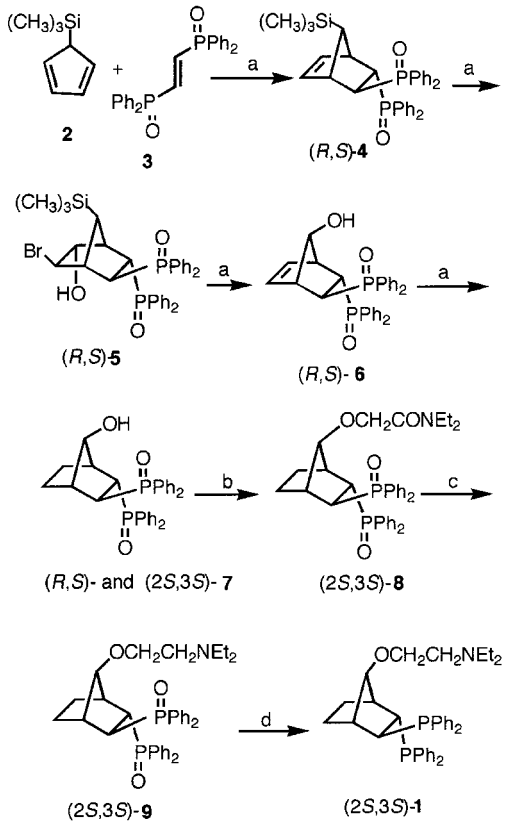
Figure 1

In connection of this work, we planned to introduce an amino group as a hetero-functional group on NORPHOS.[7] The synthetic route to the optically active bisphosphine ligand (*S*,*S*)-NORPHOS-7-NEt_2 ((*S*,*S*)-**1**) is shown in Scheme 1.

Synthesis of (2*S*,3*S*)-**7** was carried out according to the methods in our previous work[3] and the following etherification of (*S*,*S*)-**7** with N,N-diethyl chloroacetamide gave (*S*,*S*)-**8** in 81% yield. Reduction of (*S*,*S*)-**8** with diborane at 80 °C gave (*S*,*S*)-**9** in 70% yield. Final reduction of the phosphine oxide **9** 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 (*S*,*S*)-NORPHOS-7-NEt_2 ((*S*,*S*)-**1**)[8] in 68% yield.

Asymmetric allylic substitution reaction of 1,3-diphenyl-2-propenyl pivalate **10** (0.5 mmol) with the nucleophile produced by mixing dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and lithium acetate as a catalyst was carried out at room temperature for 48 hr using a palladium complex generated in situ from a chiral ligand (0.05 mmol) and $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.0125 mmol) as catalyst.[9] The results are summarized in the Table.

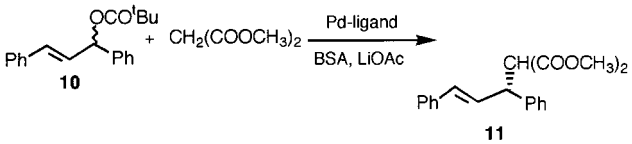
The Pd-catalyzed asymmetric allylic alkylation of **10** with (*S*,*S*)-**1** (**M**-Chirality)[10] gave (*R*)-**11** of the same absolute configuration as the product (*R*)-**11** obtained with (*R*,*R*)-NORPHOS (**P**-Chirality). This result clearly indicates the interaction of the amino group on the ligand with the incoming nucleophile and the importance of the neighboring participation in enantioselection of asymmetric allylic alkylation.[11,12] Another explanation that the NORPHOS-7-NEt_2 ligand forms an aminophosphine-Pd complex[13] to catalyze the asymmetric allylic alkylation with high optical yield may be unreasonable, because of the



Reagent, Condition: a. reference 3 b. NaH, $ClCH_2CONEt_2$, y. 81% c. BH_3, y. 70 % d. $HSiCl_3$, Et_3N, toluene, y. 68%

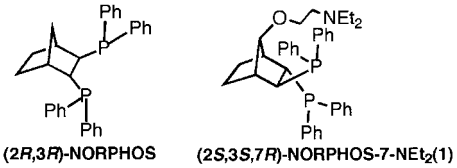
Scheme 1

Table. (2*S*,3*S*,7*R*)-NORPHOS-7-NEt_2-Pd Complex-Catalyzed Allylic Substitution Reaction Forming a C-C Bond



Chiral ligand	P/M chirality	solvent	yield[b]	e.e.(%)[c](Config.)
(2*R*,3*R*)-Norphos	p	THF	50	16 (*R*)
(2*S*,3*S*,7*R*)-Norphos-7-NEt_2(**1**)	M	THF	52	76 (*R*)
(2*R*,3*R*)-Norphos	p	CH_2Cl_2	89	73 (*R*)
(2*S*,3*S*,7*R*)-Norphos-7-NEt_2(**1**)	M	CH_2Cl_2	90	99 (*R*)

a) All asymmetric allylic reactions were carried out at room temperature for 48 hr in the presence of 5mol% of a catalyst prepared in situ by mixing $[Pd(\pi\text{-}C_3H_5)Cl]_2$ and the chiral ligand in a ratio of 1 : 4.
b) Isolated yield by preparative TLC on silica gel.
c) Determined by HPLC analysis with a stationary-phase column (DAISEL CHIRAL AD)



(2*R*,3*R*)-NORPHOS **(2*S*,3*S*,7*R*)-NORPHOS-7-NEt_2(1)**

conformational flexibility of the eight-membered aminophosphine-Pd complex and also the lack of the asymmetric environment near the amino group.

In summary, a new bisphosphine ligand, (2*S*,3*S*,7*R*)-NORPHOS-7-NEt_2((*S*,*S*)-**1**) having an amino group as a neighboring participating group was synthesized and found to be efficient for palladium complex-catalyzed asymmetric allylic alkylation.

Acknowledgement

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References and Notes

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(12) BHMP-7X having a carboxyl group as a neighboring participating group was found to be efficient for asymmetric allylic amination of **10** to give (*R*)-amino-compounds in high optical yield by interaction of the carboxylate group and the amino group.[3-5]

(13) Efficient aminophosphine ligands form five- or six-membered Pd complexes and have the asymmetric environment near the amino group.[9] (P. van Matt, and A. Pfaltz, *Angew. Chem., Int. Ed. Engl*., **32**, 566 (1993), J. Sprinz, M. Kiefer, G. Helmchen, and M. Reggelin, *Tetrahedron Lett*., **35**, 1523 (1994), H. Kubota, and K. Koga, *Tetrahedron Lett*., **35**, 6689 (1994)).