Tetrahedron Letters Vol. 21, pp 79 - 82 0040-4039/80/0101-0079$02.00/0
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CHIRAL β-DIMETHYLAMINOALKYLPHOSPHINES. HIGHLY EFFICIENT LIGANDS FOR A NICKEL COMPLEX CATALYZED ASYMMETRIC GRIGNARD CROSS-COUPLING REACTION

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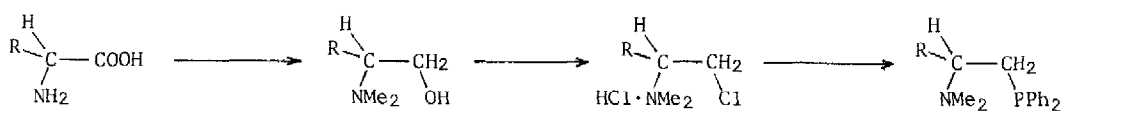
Summary: Chiral β-dimethylaminoalkylphosphines were prepared starting with amino acids, (*S*)-alanine, (*S*)-phenylalanine, (*R*)-phenylglycine, (*S*)-valine, and (*R*)-*tert*-leucine. The chiral phosphines were found to be highly efficient ligands for a nickel catalyzed asymmetric Grignard cross-coupling reaction (38~94% optical yield).

Asymmetric C-C bond forming reactions are of great significance for the synthesis of optically active compounds,[1] and the use of chiral transition metal catalysts for such reactions[2] has lately attracted considerable attention owing to a number of well-recognized advantages of catalytic asymmetric synthesis.[1b]

In our recent study on asymmetric Grignard cross-coupling catalyzed by nickel-phosphine complexes, we have shown that chiral (aminoalkylferrocenyl)phosphines are effective ligands to produce a coupling product of ~60% ee and the presence of the dimethylamino group in the chiral ligands is responsible for the high degree of asymmetric induction.[3] On the basis of the data, we have devoted attention to the design and preparation of new phosphine ligands of higher ability for the asymmetric Grignard cross-coupling. Now we report that very high stereoselectivity was attained in the Grignard cross-coupling by the use of new chiral ligands, β-aminoalkylphosphines readily prepared from amino acids.

The β-aminoalkylphosphines[4] were prepared by a sequence of reactions starting with amino acids (1), viz, (*S*)-alanine (1a), (*S*)-phenylalanine (1b), (*R*)-phenylglycine (1c), (*S*)-valine (1d), and (*R*)-*tert*-leucine (1e),[5] as shown in Scheme I. *N*-Methylation of 1 by reductive condensation with formaldehyde and hydrogen in the presence of Pd-C,[6] followed by reduction with

Scheme I



1a : R = Me (*S*)
1b : R = CH_2Ph (*S*)
1c : R = Ph (*R*)
1d : R = *i*-Pr (*S*)
1e : R = *t*-Bu (*R*)

2

3

4a : (*S*)-Alaphos
4b : (*S*)-Phephos
4c : (*R*)-PhGlyphos
4d : (*S*)-Valphos
4e : (*R*)-*t*-Leuphos

Table 1. Asymmetric Cross-Coupling of 1-Phenylethylmagnesium Chloride (5) with Vinyl Bromide (6) Catalyzed by Chiral Phosphine-Nickel Complexes.[a]

Chiral ligand	Yield[b] (%)	$[\alpha]_D^{22}$ of 7[c] (neat)	Optical purity (%) (Configuration)		
(*S*)-Alaphos (4a)	98	+2.25	38		(*S*)
(*S*)-Phephos (4b)	98	+4.19	71		(*S*)
(*R*)-PhGlyphos (4c)	97	-4.11	70		(*R*)
(*S*)-Valphos (4d)	96	+4.78	81		(*S*)
(*R*)-*t*-Leuphos (4e)[d]	96	-4.92	83	(94)[e]	(*R*)
(*S*)-8[f]	97	-0.40	7	(25)[e]	(*R*)
(*S*)-9	98	0	0		

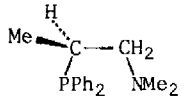
[a] To a mixture of 6 (20 mmol), $NiCl_2$ (0.10 mmol), and a chiral phosphine (0.10 mmol) was added 5 (30∿40 mmol) in ether (30∿40 ml) at -78°. The mixture was kept at 0° for 2 days. [b] Yields based on 6 were determined by GLC. Isolated yields by preparative GLC were over 70%. [c] Optically pure (*R*)-3-phenyl-1-butene (7) has $[\alpha]_D^{22}$ -5.91° ± 0.04° (neat); T. Hayashi, M. Konishi, S. Kawakami, M. Fukushima, and M. Kumada, to be published. [d] See ref. 11. [e] Optical yields corrected for the optical purity of the phosphine ligand used. [f] 8 of 27% optical purity was used.

lithium aluminum hydride in THF[7] gave β-dimethylaminoalkyl alcohols (2), which were then converted by treatment with hydrogen chloride and thionyl chloride in chloroform[8] to β-dimethylaminoalkyl chloride hydrochlorides (3). The reaction of 3 with diphenylphosphine and potassium *tert*-butoxide in THF[9] gave β-dimethylaminoalkyldiphenylphosphines (4) (40∿50% overall yield from 1); (*S*)-4a; $[\alpha]_D^{25}$ -47.2°,[10] (*S*)-4b; $[\alpha]_D^{25}$ +32.9°,[10] (*R*)-4c; $[\alpha]_D^{25}$ +40.1°,[10] (*S*)-4d; $[\alpha]_D^{25}$ +12.5°,[10] (*R*)-4e;[11] $[\alpha]_D^{25}$ -114.8°.[10]

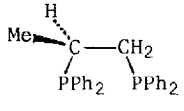
Using these chiral phosphines as ligands, the nickel-catalyzed cross-coupling[12] of 1-phenylethylmagnesium chloride (5) with vinyl bromide (6) was carried out (eq. 1). The reaction

$$\underset{dl\text{-}5}{PhMeCHMgCl} + \underset{6}{CH_2{=}CHBr} \xrightarrow{[Ni\text{-}L^*]} \underset{7}{PhMe\overset{*}{C}HCH{=}CH_2} \qquad (1)$$

conditions and results are summarized in Table 1, which also contains, for comparison, data obtained with (*S*)-2-diphenylphosphinopropyldimethylamine (8)[13] and (*S*)-1,2-bis(diphenylphosphino)propane (9).[14]

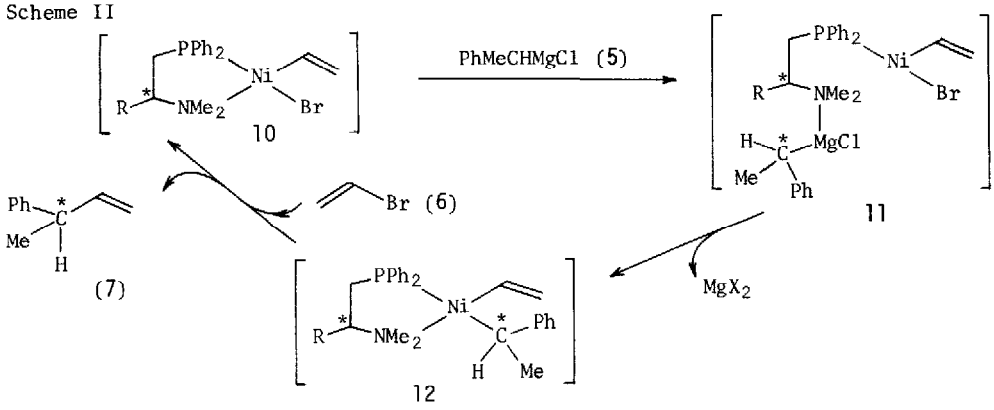


(*S*)-8



(*S*)-9

Scheme II



Some of the main features observed in Table 1 are as follows: (1) The coupling product 7 of very high optical purity was obtained when Phephos (4b), PhGlyphos (4c), Valphos (4d), or *t*-Leuphos (4e) was used as a ligand. The stereoselectivity of over 70% achieved here is the highest thus far reported for the asymmetric Grignard cross-coupling. The extremely high ability of *t*-Leuphos (4e) to cause asymmetric induction (94%) is particularly noteworthy. (2) The phosphine ligand (4) with the larger substituent at the chiral carbon atom induced the higher stereoselectivity, that is, the order of efficiency for asymmetric induction is 4e (R = *t*-Bu) > 4d (R = *i*-Pr) > 4b (R = CH_2Ph) ≈ 4c (R = Ph) > 4a (R = Me). (3) Lower stereoselectivity was observed in the reaction with 8 than with 4a. This indicates that the ligand with a chiral carbon center at the dimethylamino group is more effective than that with a chiral carbon center at the diphenylphosphino group. (4) The use of 9 for the present reaction resulted in the formation of the racemic coupling product only, although 9 has been successfully used for asymmetric hydrogenation of α-amidoacrylic acids.[14]

It is clear from the results that the presence of the dimethylamino group in the phosphine ligands is playing a key role in this system, and the following mechanism (Scheme II), which appears consistent with all the features above, may be proposed based on the catalytic cycle assumed for the nickel-catalyzed Grignard cross-coupling.[12]

When the Grignard reagent approaches the organonickel intermediate 10,[15] the dimethylamino group in the aminophosphine ligand dissociates from the nickel and coordinates with the magnesium atom in the Grignard reagent to form the diastereomeric transition state 11. The coordination must occur selectively with one of the enantiomers of the Grignard reagent that, probably, always exists in a racemic form,[3] and the selectivity is affected by the steric bulkiness of the alkyl group substituted at the chiral carbon on the aminophosphine ligand. Subsequent attack of the 1-phenylethyl group on the nickel leads to the diorganonickel intermediate 12. Reductive elimination of optically active coupling product 7 from 12 and oxidative addition of 6 reproduces 10. Although the stereochemistry of the transmetallation and the reductive elimination in this system has not been elucidated, these processes must occur with high stereospecificity since the optical purity of the coupling product is very high.

The use of this asymmetric Grignard cross-coupling for the synthesis of optically active terpenes and biologically active compounds will be the subject of future communications.

Acknowledgement We thank the Ministry of Education, Japan, for Grant-in-Aid (No. 311709, 355370) and Asahi Glass Foundation of the Contribution to Industrial Technology for financial support. We are grateful to Prof. K. Koga and Dr. K. Tomioka (The University of Tokyo) for helpful suggestions for the preparation of optically active *tert*-leucine.

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(9) M. E. Wilson, R. G. Nuzzo, and G. M. Whitesides, *J. Am. Chem. Soc.*, 100, 2269 (1978).

(10) Specific rotation in benzene, *c* 0.3-1.5.

(11) Prepared from (*R*)-1e of 88% ee ($[\alpha]_D^{20}$ +8.94° (*c* 5, H_2O)).

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(13) Prepared from (*R*)-1-dimethylamino-2-chloropropane hydrochloride which was obtained by thermal rearrangement of 3a. The enantiomeric purity of (*S*)-8a ($[\alpha]_D^{25}$ -18° (*c* 1, benzene)) was determined to be 27% by NMR spectra of its phosphine oxide in the presence of $Eu(dcm)_3$.

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(15) An attempt to isolate nickel complexes of the aminoalkylphosphines 4 has been unsuccessful. Dichloro(aminoalkylphosphine)palladium(II), prepared from 4 and dichlorobis(acetonitrile)-palladium(II), showed almost the same catalytic activity and stereoselectivity as the nickel catalyst, and the NMR spectra of the palladium complex indicated that the aminoalkylphosphine ligand coordinates to palladium with both phosphorus and nitrogen atoms.

(Received in Japan 27 September 1979)