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ASYMMETRIC GRIGNARD CROSS-COUPLING BY MEANS OF POLYMER-SUPPORTED OPTICALLY ACTIVE β-DIMETHYLAMINOALKYLPHOSPHINE-NICKEL CATALYSTS

Tamio Hayashi, Nobuo Nagashima, and Makoto Kumada*

Department of Synthetic Chemistry, Kyoto University, Kyoto 606, Japan

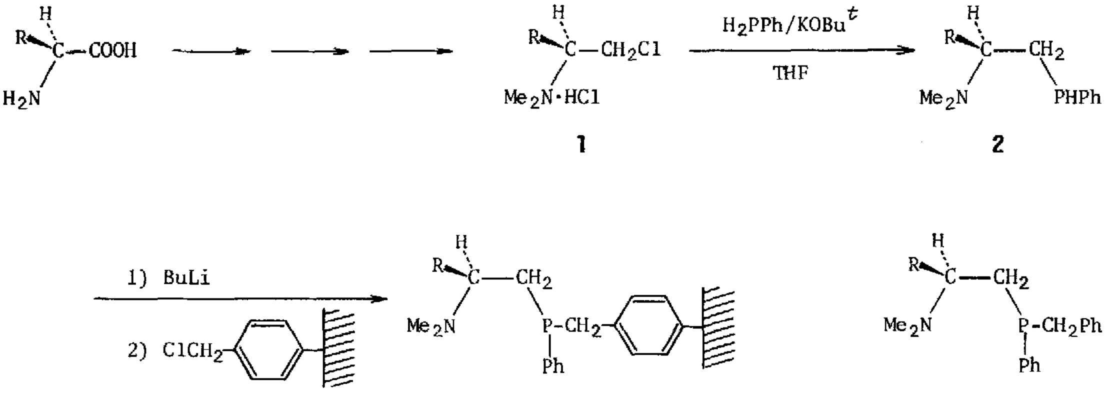
Summary: New polymer ligands containing β-dimethylaminoalkylphosphines were prepared using chloromethylated polystyrene, and the ligands were used for nickel-catalyzed asymmetric cross-coupling of *sec*-alkyl Grignard reagents with vinyl bromide to yield coupling products of ∿50% ee.

Polymer-supported homogeneous catalysts have recently attracted considerable attention, having both of the advantages of homogeneous and heterogeneous catalysts.[1] One of the advantages of homogeneous catalysts is that the properties can be controlled by variations of steric and electronic factors in the ligand coordinated to the transition metal center, and a chiral catalyst with optically active ligands is a typical representative of the well-designed homogeneous catalysts. Several attempts have been made[2~6] to attach chiral bisphosphine-rhodium complexes to a solid support and they have been used for asymmetric hydrosilylation, hydrogenation and hydroformylation.

Optically active β-dimethylaminoalkyldiphenylphosphines derived from α-amino acids have proved to be effective ligands for nickel-catalyzed asymmetric cross-coupling of a secondary alkyl Grignard reagent with vinyl bromide to give a coupling product of over 80% ee.[7a] Here we report the synthesis of new polymer ligands, polystyrene-bound β-dimethylaminoalkylphosphines, and their use in the asymmetric Grignard cross-coupling.

The polymer-supported β-aminoalkylphosphines were prepared as shown in Scheme I. (*S*)-2-dimethylamino-3-methylbutyl chloride hydrochloride (**1a**),[7a] prepared from (*S*)-valine, was treated with potassium phenylphosphide generated in situ from potassium *t*-butoxide (2.3 equiv) and phenylphosphine (1.0 equiv) in THF to give (*S*)-2-dimethylamino-3-methylbutylphenylphosphine (**2a**)

Scheme I

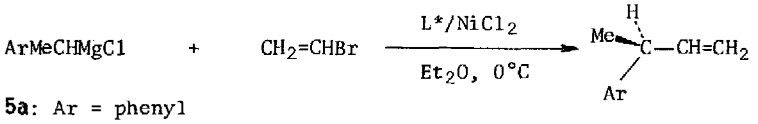


3a: R = *i*-Pr
3b: R = CH_2Ph

4a: R = *i*-Pr
4b: R = CH_2Ph

in 97% yield. Butyllithium (1.2 equiv) in hexane was added to a solution of the phosphine **2a** in THF. To the resulting solution of lithium phosphide was added chloromethylated polystyrene (1.0 equiv) (0.97 mequiv of Cl/g, 200-400 mesh, 2% divinylbenzene).[8] The mixture was kept stirring at room temperature for 20 hr, and then hydrolyzed with water. The polymer was filtered, washed successively with methanol and benzene, and dried in vacuo. The elemental analysis of the polymer **3a**[9] showed that 67% of the chloride was substituted with the phosphino group and **3a** contained ca. 0.5 mequiv of aminoalkylphosphine unit (P-N) per gram. Starting with **1b**, polymer ligand **3b**[10] was obtained in a similar manner, which contained ca. 0.7 mequiv of P-N/g. Monomeric ligands, β-dimethylaminoalkylbenzylphenylphosphines **4**,[11] analogous to the polymer-supported ligands **3**, were also prepared by treatment of **2** with butyllithium and benzyl chloride.

The cross-coupling of 1-arylethylmagnesium chloride (**5**) with vinyl bromide was investigated using the polymer-supported phosphine ligands **3** (eq. 1). A nickel catalyst prepared in situ



$$\mathrm{ArMeCHMgCl} + \mathrm{CH_2{=}CHBr} \xrightarrow[\mathrm{Et_2O,\ 0^\circ C}]{\mathrm{L^*/NiCl_2}} \mathrm{Me(H)(Ar)C{-}CH{=}CH_2} \qquad (1)$$

5a: Ar = phenyl
5b: Ar = *p*-tolyl
5c: Ar = 2-naphthyl

6a-c

Table 1. Asymmetric Grignard Cross-Coupling with Polymer-Supported β-Dimethylaminoalkylphosphines.

Grignard reagent	Chiral ligand	Time (days)	Yield[a] (%)	$[\alpha]_D^b$	% ee (Configuration)
5a	**3a**	2	73	+2.92°	49 (*S*)
5a	**3a** (reused)[c]	3	93	+2.82°	48 (*S*)
5a	**3b**	6	92	+2.04°	35 (*S*)
5a	**4a**	2	94	+3.13°	53 (*S*)
5a	**4b**	2	96	+2.89°	49 (*S*)
5b	**3a**	7	91	+4.03°	50 (*S*)
5c	**3a**	4	80	+3.56°	34 (*S*)

[a] Yields based on vinyl bromide were determined by GLC. [b] The specific rotations of **6** have been reported as follows: (*R*)-**6a**; $[\alpha]_D^{22}$ -5.91° ±0.04° (neat), ref. 7; (*R*)-**6b** (66% ee), $[\alpha]_D^{22}$ -5.38° (neat), K. Tamao, T. Hayashi, H. Matsumoto, H. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 2155 (1979); (*R*)-**6c** (95% ee), $[\alpha]_D^{25}$ -9.83° (neat), R. Menicagli, O. Piccolo, L. Lardicci, and M. L. Wis, *Tetrahedron*, **35**, 1301 (1979).
[c] See text.

from nickel chloride and **3** was conveniently used for the asymmetric cross-coupling. It is not necessary to isolate the polymer-supported nickel complex, since nickel chloride free from phosphine ligands is almost inactive for the present cross-coupling and therefore it does not affect the optical purity of the coupling product.

To a mixture of $NiCl_2$ (0.10 mmol) and **3** (0.15 mequiv of β-aminoalkylphosphine unit) was added at -78°C vinyl bromide (20 mmol) and an ether solution of a Grignard reagent (40 mmol). The mixture was stirred at 0°C under an argon atmosphere. Hydrolysis with diluted hydrochloric acid followed by the usual workup[7] gave coupling product **6**. The results are summarized in Table 1.

The rates of the cross-coupling with polymer ligand **3** were smaller than those with monomar ligand **4** and the reaction required 3-7 days to achieve high yields, but the stereocontrolling ability of **3** was comparable with that of **4**. Thus, the optical purity of **6a** obtained with the polymer ligand **3a** (49% *S*) in the reaction of 1-phenylethyl Grignard reagent (**5a**) is quite similar to that obtained with monomer ligand **4a** (53% *S*). The polymer ligand **3a** was also effective for the reaction of 1-(*p*-tolyl)ethyl (**5b**) and 1-(2-naphthyl)ethyl (**5c**) Grignard reagents to give the corresponding coupling products of *S* configuration.

The polymer-supported nickel catalyst could be recovered by quick filtration in the air before hydrolysis, and reused with no loss in catalytic activity or stereoselectivity for the present coupling reaction. The polymer recovered after acid hydrolysis did not catalyze the reaction.

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(8) Bio-Beads S-X1, BIO-RAD Laboratories.
(9) Found: H, 7.82; C, 87.89; N, 0.81; Cl, 1.15; P, 1.46%.
(10) Found: H, 7.69; C, 88.36; N, 1.06; Cl, 0.73; P, 2.00%.
(11) The benzylphosphines **4a** and **4b** were isolated as viscous oily substances and readily oxidized in the air to form phosphine oxides of **4** as white solid. The phosphine oxide of **4a**, Found: C, 72.76; H, 8.53; N, 4.42; P, 9.03. Calcd. for $C_{20}H_{28}PNO$: C, 72.92; H, 8.57; N, 4.25; P, 9.40%. The phosphine oxide of **4b**, Found: C, 76.13; H, 7.69; N, 3.83; P, 8.12. Calcd. for $C_{24}H_{28}PNO$: C, 76.37; H, 7.48; N, 3.71; P, 8.21%. The NMR spectra indicated that **4a** and **4b** consisted of a one to one mixture of diastereoisomers, that is, the configuration of the phosphorus center is 50% *R* and 50% *S*.

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