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Asymmetric Grignard Cross-Coupling Reaction Using Chiral Ligands Derived from Carbohydrates

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Chiral diphenylphosphine and diphenylphosphinite derivatives of carbohydrates such as D-glucose, D-galactose, and L-rhamnose were used as the ligand of metal catalysts for asymmetric Grignard cross-coupling reaction. Coupling of *s*-butylmagnesium bromide with bromobenzene was carried out in the presence of nickel or palladium chloride with the chiral ligand. The highest optical yield was observed when D-galactose ligand was used.

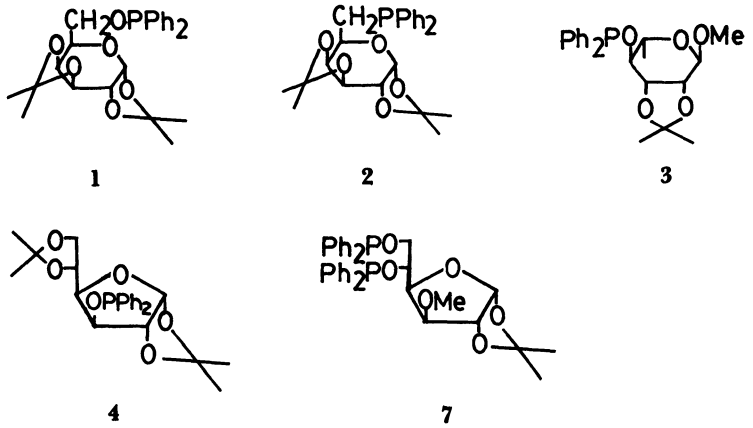
Investigation of good chiral ligands is very important field in catalytic asymmetric reactions such as asymmetric hydrogenations and asymmetric coupling reactions.[1] A wide variety of ligands were used for asymmetric hydrogenations, where many monodentate and bidentate chiral phosphines such as CAMP, DIOP, and Norphos afforded chiral products in excellent optical yields.[2] For asymmetric Grignard cross-coupling reactions the ligands gave the product in poor to fair optical yields.[3] Chiral carbohydrate ligands, which can be easily prepared from readily available carbohydrates without optical resolution, are not so well investigated.[1),4] Some of the ligands showed potential ability for asymmetric induction in prochiral olefins.[4] To spread the application of carbohydrate ligands in the field for asymmetric synthesis we now tried to use them for cross-coupling reactions.

Coupling reactions of 1-phenylethylmagnesium halides with vinyl halides were successful using ferrocene[5] and amino acid derivatives[6] as the chiral ligand. But couplings of *s*-butylmagnesium halides with halobenzenes were unsuccessful so far. The coupling reactions, where phenyl groups in the Grignard reagents are absent, are competed with isomerization and elimination reactions.[7,8] This paper deals with asymmetric Grignard cross-coupling reaction using carbohydrate ligands of catalysts.

Carbohydrates exist widely in nature and they have some advantages for asymmetric synthesis in such properties as ready availability, rigidity of the structure, and chirality of the framework. Some ligands derived from carbohydrates were used for asymmetrical catalytic hydrogenations,[2,4,9,10] however, they were scarcely applied to asymmetric coupling reactions.[3] It is suggested that diphenylphosphinite derivatives afford higher optical yields than corresponding diphenylphosphine derivatives do, and that diphenylphosphinite derivatives can easily be synthesized through a shorter pathway than corresponding diphenylphosphine derivatives by at least two steps from starting carbohydrates having free hydroxyl groups.

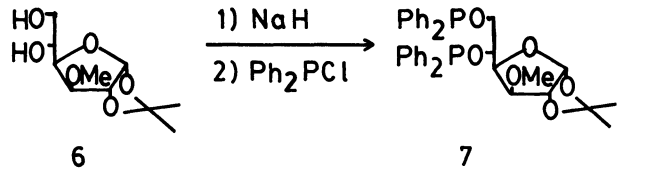
Results and Discussion

Synthesis of Chiral Phosphino Ligands from Carbohydrates. Compounds **1**, **2**; **3**; and **4**, **7** were prepared from D-galactose; L-rhamnose; and D-glucose, respectively by known methods.[10] Reaction of glucose **6** with diphenylphosphinous chloride in the presence of sodium hydride in dry ether afforded not only diphosphino compound **7**, but also monophosphino compound **5** (Eq. 1). These ligands were immediately used for coupling reaction without isolation.



1 2 3 4 7

Scheme 1.



6 7

monophosphino deriv. 5 (1)

Asymmetric Grignard Cross-Coupling Reaction. Nickel- or palladium-catalyzed cross-coupling reaction of *s*-butylmagnesium bromide **8** with bromobenzene **9** using chiral ligands was carried out (Eq. 2). The reaction conditions and results are summarized in Table 1.

$$\underset{\mathbf{8}}{s\text{-BuMgBr}} + \underset{\mathbf{9}}{\text{PhBr}} \longrightarrow \underset{\mathbf{10}}{s\text{-BuPh}} + \underset{\mathbf{11}}{n\text{-BuPh}} \quad (2)$$

Table 1 shows that non-isomerized product **10** was obtained in higher yield than isomerized product **11**. The ratio of **10** to **11** obtained is higher than that reported using monodentate triphenylphosphine ligand.[11] This reason may be attributable to the property of the ligand having P–O–C bond, where electron density of phosphorus atom is lower than that of P–C bond.[7] Indeed the diphenylphosphinite ligand used in Entries 1 and 2 afforded less isomerized product than the corresponding diphenylphosphine ligand did in Entries 3 and 4. In asymmetric induction, the carbohydrate ligand having phosphorus atom out of the hemiacetal ring induced higher optical yield than the ligand having phosphorus atom in the hemiacetal ring did. Especially, D-galactose ligands **1** and **2** afforded the highest optical yields (Entries 2 and 3). These results confirmed that carbohydrate ligands are accessible for asymmetric cross-coupling reaction as chiral sources.

Experimental

Measurements. ^{1}H NMR spectra were measured on a Hitachi R-24B (60 MHz) spectrometer with tetramethylsilane as an internal standard, and IR spectra on a Japan Spectroscopic Co., Ltd., A-3 infrared spectrometer. Optical rotations were measured on a Japan Spectroscopic Co., Ltd., DIP-4 digital polarimeter. Isolation of coupling products was performed by a Yanaco Gas Chromatograph G 1800, equipped with a 1.5 m stainless steel column packed with silicone gum SE30 (30% on chromosorb W) at 100 °C (column) and 175 °C (injection).

Preparation of 6-*O*-(Diphenylphosphino)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1). To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose 0.39 g (1.50 mmol) in dry ether was added 72 mg (1.8 mmol) of sodium hydride, and the mixture was stirred for 12 h at room temperature under argon atmosphere. Diphenylphosphinous chloride (1.5 equiv) was added to the reaction mixture through a septum cap. After 24 h the mixture was filtered and the filtrate was successively washed with water and brine. The solution was dried over sodium sulfate and evaporated in vacuo. Crude product **1** (0.50 g) was obtained

Table 1. Asymmetric Cross-Coupling Reaction of **8** with **9**[a]

Entry	Ligand	Metal	Conversion/%[b]	Chemical yield/%[c]	
				10	**11**
1	**1**	Pd	91	17	4.3
2	**1**	Ni	58	15	Trace
3	**2**	Ni	98	5.5	9.4
4	**2**	Pd	77	6.6	9.6
5	**7**	Pd	96	3.4	3.6
6	**4**	Ni	54	5.1	2.1
7	**4**	Pd	90	10	10
8	**3**	Ni	69	7.0	3.0
9	**3**	Pd	76	20	4.3

Entry	$[\alpha]_D^t$/° (Concentration)[d]	Optical yield/%[e] (Configuration)
1	$[\alpha]^{16}$= −2.48 (*c* 1.05)	8.5 (*R*)
2	$[\alpha]^{20}$=−15.6 (*c* 0.397)	53 (*R*)
3	$[\alpha]^{20}$=+28.9 (*c* 0.993)	99 (*S*)
4	$[\alpha]^{21}$= −1.73 (*c* 0.980)	5.9 (*R*)
5	$[\alpha]^{21}$= −9.60 (*c* 0.177)	33 (*R*)
6	$[\alpha]^{30}$= −3.58 (*c* 0.520)	12 (*R*)
7	$[\alpha]^{16}$= −2.73 (*c* 0.880)	9.3 (*R*)
8	$[\alpha]^{16}$= −3.35 (*c* 0.925)	11 (*R*)
9	$[\alpha]^{29}$= −1.08 (*c* 1.15)	3.7 (*R*)

a) Reaction condition: ratio of **8** to **9** was 2:1 except for Entry 2 (**8** to **9** was 1.05:1 for Entry 2); and ratio of **9** to MCl_2 was 50:1. Reactions were carried out for about 40 h at 35 °C under argon atmosphere. b) Conversion was calculated on a basis of **9** recovered. c) Yield was calculated on a basis of **9** reacted. d) Benzene was used as the solvent. Less than 7% concentration dependence of $[\alpha]_D^t$ value was observed. e) Optical yield was calculated based on the specific rotation of (*S*)-2-phenylbutane: $[\alpha]_D^{25}$=+29.26° (neat).[8]

in 74% yield. The purity was checked by TLC on silica gel (eluent: ethyl acetate; R_f=0.74). IR ν_{max}^{neat} (cm^{-1}), 1442 (P-Ph), 1080 (P-O-C). ^1H NMR ($CDCl_3$) δ=1.32, 1.42, 1.46, (3s, 12H, $2CMe_2$), 3.7—4.8 (m, 6H, $C_{2-6,6'}$-H), 5.56 (d, 1H, $J_{H_1H_2}$=5.0 Hz, C_1-H), and 7.2—7.7 (m, 10H, PPh_2).[10b]

Preparation of Other Diphenylphosphinite Ligands. Methyl 4-*O*-(diphenylphosphino)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**3**), 3-*O*-(diphenylphosphino)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**), and 5,6-di-*O*-(diphenylphosphino)-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (**7**) were prepared almost in pure form except **7** by the same procedure as above from the corresponding precursors. Crude product **7** showed two spots of TLC on silica gel (R_f; 0.88 and 0.71 (ethyl acetate)). They were monophosphino and diphosphino derivatives, respectively, and were used for the coupling reaction without isolation. Spectral data for **7**: ^1H NMR ($CDCl_3$) δ=1.20, 1.31 (2s, 6H, CMe_2), 3.30 (s, 3H, OMe), 3.5—4.4 (m, 5H, $C_{3-6,6'}$-H), 4.42 (d, 1H, $J_{H_1H_2}$= 3.5 Hz, C_2-H), 5.75 (d, 1H, $J_{H_1H_2}$=3.5 Hz, C_1-H), 7.0—8.0 (m, 20H, $2PPh_2$); IR ν_{max}^{neat} (cm^{-1}), 1442 (P-Ph), 1030 (P-O-C); MS *m/z*, 602 (M^+).

Preparation of 6-*C*-(Diphenylphosphino)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2). Through a septum cap a solution of 0.248 g (0.60 mmol) of the 6-*O*-*p*-toluenesulfonyl derivative in dry THF was added to refluxing THF solution of lithium diphenylphosphinide prepared by the treatment of 0.157 g (0.60 mmol) of triphenylphosphine with lithium under argon atmosphere.[11] The mixture was further refluxed for 4 h and cooled to room temperature. The product was extracted with ether and washed with water and brine. The solution was dried with sodium sulfate and evaporated in vacuo to give 0.257 g (quantitative yield) of crude **2**, which was contaminated with the tosylate, used without further purification. IR ν_{max}^{neat} (cm^{-1}), 1440 (P-Ph), 722 (C-P). ^1H NMR ($CDCl_3$) δ=1.30, 1.35, 1.46, 1.50 (4s, 12H, $2CMe_2$), 1.7—2.2 (m, 2H, $C_{6,6'}$-H), 3.6—4.7 (m, 4H, C_{2-5}-H), 5.45 (d, 1H, $J_{H_1H_2}$=5.0 Hz, C_1-H), 7.2—8.2 (m, 10H, PPh_2).

General Procedure for Coupling Reactions. In a 50 ml two-necked flask equipped with a stirring bar, a septum cap, and a stopcock was placed 13.0 mg of nickel chloride (0.1 mmol=2.0 mol%) or 17.7 mg of palladium chloride. The reaction vessel was filled with argon after evacuation and a solution of 0.2 mmol of ligand **1**, **2**, **3**, or **4**, or of 0.1 mmol of ligand **7** in freshly distilled 2—3 ml of THF was added via syringe through the ceptum cap. The reaction mass was refluxed for 1 h and cooled to 0 °C. To the solution were added 0.52 ml (5.0 mmol) of bromobenzene and solution of *s*-butylmagnesium bromide (prepared from 10 mmol of *s*-butyl bromide and magnesium in 10 ml of dry ether under nitrogen atmosphere) via a syringe through the septum cap. The reaction mixture was again refluxed for about 40 h and hydrolyzed with 8 ml of 10% hydrochloric acid. Extraction of the product with ether (6 ml×3) followed by successive washing the organic layer with aq. sodium hydrogencarbonate (4 ml×2) and water (5 ml), drying over anhydrous sodium sulfate, and removal of low boiling materials (bp<120 °C) afforded crude analytical sample. Unreacted bromobenzene and *s*- and *n*-butylbenzenes were isolated from the sample by gas chromatography. The structures of all the products were confirmed by ^1H NMR.

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