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Preparation of (*R*)-*N*,*N*-Dimethyl-1-[2-(diphenylphosphino)ferrocenyl]-2-propanamines and Asymmetric Grignard Cross-coupling Catalyzed by Nickel Complexes with the Phosphine Ligands

Tamio Hayashi, Mitsuo Konishi, Takeshi Hioki, Makoto Kumada,*
Aleksander Ratajczak,† and Halina Niedbała†
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606
† *Laboratory of Organic Chemistry, Institute of Chemistry, Silesian University, 40-006 Katowice, Poland*

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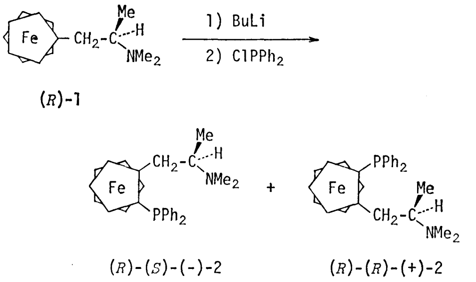
Synopsis. A pair of diastereoisomeric phosphines, (*R*)-*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]-2-propanamines, have been prepared and used as ligands for nickel-catalyzed asymmetric cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide to give 3-phenyl-1-butene of 14—15% enantiomeric excess.

We have recently prepared various kinds of chiral ferrocenylphosphines, *e.g.*, (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*R*)-PPFA], starting with *N*,*N*-dimethyl-1-ferrocenylethylamine.[1] Some of them have been found to be effective ligands for several transition metal complex catalyzed asymmetric reactions giving rise to high optical yields.[2] Here we report the preparation of new chiral ferrocenylphosphines from *N*,*N*-dimethyl-1-ferrocenyl-2-propanamine and their use as ligands for nickel-catalyzed asymmetric Grignard cross-coupling.

Results and Discussion

(*R*)-*N*,*N*-Dimethyl-1-ferrocenyl-2-propanamine[3] (**1**) (80% ee) was lithiated with an excess of butyllithium in ether, and the lithiated ferrocene was then treated with chlorodiphenylphosphine. (*R*)-*N*,*N*-Dimethyl-1-[2-(diphenylphosphino)ferrocenyl]-2-propanamines (**2**), which consisted of two diastereomeric isomers in a 1:1 ratio, were obtained in 35% yield (Eq. 1). The two isomers were isolated by alumina preparative TLC; the specific rotation of one isomer was $[\alpha]^{25}_{D}$ +187° and that of the other was $[\alpha]^{25}_{D}$ −219°. The configurations of ferrocene planar chirality of (+)- and (−)-**2** were estimated empirically[1] to be *R* and *S*, respectively. It should be noted that the lithiation of **1** is not stereoselective while the lithiation of *N*,*N*-dimethyl-1-ferrocenylethylamine has been reported to proceed with high stereoselectivity.[4]



(*R*)-1

(*R*)-(*S*)-(−)-2 (*R*)-(*R*)-(+)-2 (1)

The asymmetry inducing ability of (*R*)-(*R*)- and (*R*)-(*S*)-**2** as chiral ligands was examined in the nickel catalyzed cross-coupling of 1-phenylethylmagnesium chloride (**3**) with vinyl bromide (**4**) (Eq. 2). The results are summarized in Table 1, which also contains the results obtained with (*S*)-(*R*)-PPFA ligand.[2a] The catalysts were prepared in situ by mixing nickel chloride and a chiral ligand. The ratio of nickel to ligand did not influence the stereoselectivity, and the catalytically active species is thought to consist of nickel and **2** or PPFA in a one-to-one ratio, not in a one-to-two ratio, regardless of the initial ratio of nickel chloride to the ligand.[2i] The Table contains three significant features. (1) The optical purity of the coupling product, 3-phenyl-1-butene (**5**), obtained here with **2** (14—15% ee) is much lower than that obtained with the PPFA ligand (61% ee). (2) The ferrocene planar chirality in **2** plays a more important role than the carbon central chirality, the diastereomeric isomers (*R*)-(*R*)- and (*R*)-(*S*)-**2** giving **5** with almost the same optical purity and different configurations. (3) The phosphine ligands (*R*)-(*R*)-**2** and (*S*)-(*R*)-PPFA, both of which have the same planar chirality *R*, exhibited opposite stereoselectivity.

$$\underset{\mathbf{3}}{\underset{\mathrm{Me}}{\mathrm{PhCHMgCl}}} + \underset{\mathbf{4}}{\mathrm{CH_2{=}CHBr}} \xrightarrow{\mathbf{2}/\mathrm{NiCl_2}} \underset{\mathbf{5}}{\underset{\mathrm{Me}}{\mathrm{Ph\overset{*}{C}HCH{=}CH_2}}} \tag{2}$$

Table 1. Asymmetric cross-coupling of **3** with **4**[a)]

Chiral ligand	Yield of **5**[b)] %	$[\alpha]^{22}_{D}$ (neat)	Optical purity (%)[c)] (configuration)	
(*R*)-(*R*)-**2**[d)]	88	+0.86°	15(18)[e)]	(*S*)
(*R*)-(*S*)-**2**[d)]	77	−0.80°	14(17)[e)]	(*R*)
(*S*)-(*R*)-PPFA[f)]	95	−3.59°	61	(*R*)

a) The coupling reaction was carried out at 0 °C for 40 h. **3**:**4**:catalyst=400:200:1. b) Yields based on **4** used were determined by GLC. c) Optically pure (*R*)-(−)-3-phenyl-1-butene (**5**) has $[\alpha]^{22}_{D}$ −5.91±0.04° (neat): T. Hayashi, M. Fukushima, M. Konishi, and M. Kumada, *Tetrahedron Lett.*, **21**, 79 (1980). d) **2**:NiCl$_2$=0.8:1.0. e) Corrected for the optical purity of the phosphine ligand (80% ee). f) PPFA:NiCl$_2$=2.0:1.0.

The important role of the ferrocene planar chirality causing asymmetric induction is what has been always observed in asymmetric synthesis catalyzed by chiral ferrocenylphosphine-transition metal complexes.[2] The dimethylamino group on the ferrocene side chain has been thought to enhance the stereoselectivity by coordinating to the magnesium atom of the Grignard reagent.[2a] In ferrocenylphosphine **2** the dimethylamino group is one methylene farther away from the ferrocene nucleus than in PPFA. This greater distance between the amino group and the chiral ferrocene moiety in **2** must make the stereocontrol by coordination less effective.

Experimental

Optical rotations were measured with a Yanagimoto OR-50 polarimeter. ^{1}H NMR were measured with a JEOL MH-100 spectrometer in chloroform-*d* using tetramethylsilane as an internal standard.

(*R*)-*N*,*N*-Dimethyl-1-ferrocenyl-2-propanamine (**1**) ($[\alpha]^{20}_{546}$ $-24.2°$ (*c* 1.075, ethanol)) was prepared from (*R*)-1-ferrocenyl-2-propanamine ($[\alpha]^{20}_{546}$ $-3.29°$ (*c* 5, ethanol), 80% ee) according to the procedure previously reported,[3] which was obtained by optical resolution of the racemic amine via its tartaric acid salt.[3]

*(*R*)-*N,N-*Dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]-2-propanamine [(*R*)-(*R*)-**2**] and (*R*)-*N,N-*Dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]-2-propanamine [(*R*)-(*S*)-**2**].* To a stirred solution of 255 mg (1.1 mmol) of (*R*)-**1** (80% ee) in 2.5 ml of ether was added 3.4 ml of 1.6 M butyllithium (5.4 mmol) in hexane at room temperature under nitrogen. After 5 h stirring at room temperature, 1.3 ml (7.0 mmol) of chlorodiphenylphosphine was added at 0 °C. The reaction mixture was refluxed for 2 h, and then hydrolyzed with saturated aqueous sodium hydrogencarbonate. The resulting organic layer and benzene extracts from the aqueous layer were combined and extracted with 10% phosphoric acid. The aqueous layer was made alkaline with 10% sodium hydroxide, and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel (R_f 0.3—0.7 with 9:1 ethyl acetate–methanol) to give 160 mg (35% yield) of the product **2** as an orange-red oil. ^{1}H NMR spectrum showed that the product obtained consists of two diastereomeric isomers in one to one ratio. The two isomers were isolated by preparative TLC on alumina (3:5 chloroform–benzene). (*R*)-(*R*)-**2** (42 mg, 9%); R_f 0.7, $[\alpha]^{25}_{D}$ $+187°$ (*c* 0.82, chloroform), NMR: δ 0.65 (d, 3H, $J=7$ Hz, $\mathrm{CHC\underline{H}_3}$), 2.11 (s, 6H, $\mathrm{NC\underline{H}_3}$), 2.33—2.62 (m, 1H, $\mathrm{C\underline{H}CH_3}$), 2.63—2.82 (m, 2H, $\mathrm{C\underline{H}_2}$), 3.75—4.52 (m, 3H, $\mathrm{FeC_5\underline{H}_3}$), 3.92 (s, 5H, $\mathrm{FeC_5\underline{H}_5}$), 7.13—7.75 (m, 10H, $\mathrm{C_6\underline{H}_5}$). (*R*)-(*S*)-**2** (contaminated with 10% of (*R*)-(*R*)-**2**) (40 mg, 9%); R_f 0.6, $[\alpha]^{25}_{D}$ $-219°$ (*c* 0.78, chloroform), NMR: δ 0.78 (d, 3H, $J=7$ Hz, $\mathrm{CHC\underline{H}_3}$), 2.02 (s, 6H, $\mathrm{NC\underline{H}_3}$), 1.94—2.30 (m, 2H, $\mathrm{C\underline{H}_2}$), 2.93—3.21 (m, 1H, $\mathrm{C\underline{H}CH_3}$), 3.65—4.43 (m, 3H, $\mathrm{FeC_5\underline{H}_3}$), 3.95 (s, 5H, $\mathrm{FeC_5\underline{H}_5}$), 7.08—7.70 (m, 10H, $\mathrm{C_6\underline{H}_5}$). Found: C, 71.33; H, 6.58; N, 3.04%. Calcd for $\mathrm{C_{27}H_{31}NPFe}$: C, 71.21; H, 6.64; N, 3.08%.

Asymmetric Grignard Cross-coupling. To a 100-ml pressure glass tube containing 13 mg (0.10 mmol) of anhydrous nickel chloride and 36 mg (0.08 mmol) of **2** was added at -78 °C 2.14 g (20 mmol) of vinyl bromide and 27 ml (40 mmol) of 1.5 M 1-phenylethylmagnesium chloride in ether. The glass tube was stoppered and allowed to warm up to 0 °C. The mixture was kept standing at 0 °C for 40 h, and hydrolyzed with 10% hydrochloric acid. After usual work-up, distillation through a short Vigreux column under reduced pressure followed by purification with preparative GLC (Silicone DC-550) gave 3-phenyl-1-butene. The yields and optical rotation data are shown in Table 1.

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