CHEMISTRY LETTERS, pp. 133-136, 1975. Published by the Chemical Society of Japan

NICKEL-PHOSPHINE COMPLEX CATALYZED GRIGNARD SYNTHESIS OF STERICALLY HINDERED, UNSYMMETRICAL BIARYLS: AN APPROACH TO THE ASYMMETRIC SYNTHESIS OF BIARYL ATROPISOMERS

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Sterically hindered, unsymmetrical biaryls can be prepared by the cross-coupling reaction of *ortho*-substituted aryl Grignard reagents with aryl halides in the presence of nickel-phosphine complexes as catalysts. Asymmetric synthesis of biaryl atropisomers has been accomplished with a chiral phosphine-nickel catalyst.

Biaryls are prepared by (1) the Ullmann reaction[1)] or Semmelhack's reaction[2)] from aryl halides, (2) the Gomberg reaction and variations thereof,[3)] (3) photolysis of aryl iodides[4)] or arylthallium compounds[5)] in benzene, or (4) coupling of aryl Grignard or lithium reagents with various kinds of metal halides.[6)] Most of them are, however, not suitable for the preparation of *ortho*-substituted, unsymmetrical biaryls with substituents on both rings.

In 1972, Corriu and Masse[7)] and we[8)] reported the selective cross-coupling reaction of Grignard reagents with aryl and alkenyl halides in the presence of nickel-phosphine complexes as catalysts. For this catalysis we proposed a mechanism involving a labile diorgano-nickel complex as a key intermediate. Since that time we have been interested in examining the possibility of catalytic coupling between sterically hindered *ortho*-substituted aryl-Grignard reagents and aryl halides of similar type,[9)] because it has long been recognized that *ortho*-substituted aryl-nickel complexes are of high kinetic stability.[10)]

We find that the reaction, rather surprisingly, does proceed smoothly. Examination of representative results summarized in Table reveals several features. The mesityl Grignard reagent reacts very easily with a variety of aryl bromides, including *ortho*-substituted halides, to give unsymmetrical biaryls in high yield and in high purity. Chlorobenzene is reluctant to react with the mesityl Grignard reagent. The reaction of mesityl bromide with the phenyl Grignard reagent proceeds rather slowly. Better yields can be obtained from a combination of a hindered Grignard reagent and a less hindered bromide. Triphenylphosphine seems to be more effective than bidentate phosphines as ligand in the catalyst.

Although the range of possible aromatic nuclear substituents is rather limited, the present procedure may open a facile, useful method for the synthesis of certain *ortho*-substituted, unsymmetrical biaryls.[11)]

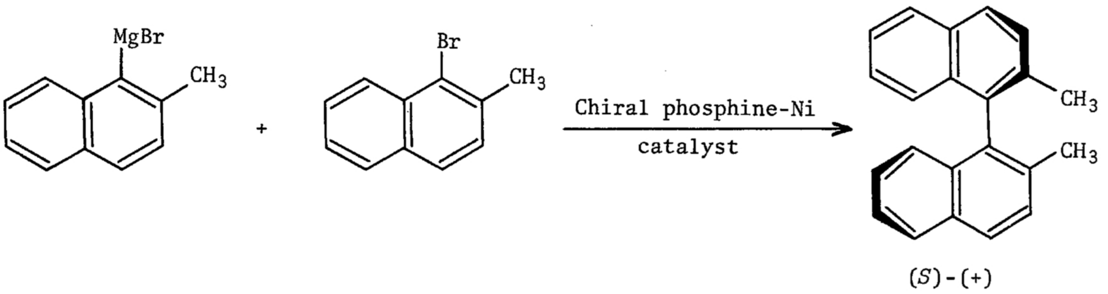
Table. Cross-coupling Reactions of *ortho*-substituted Aryl Grignard Reagents with Halides in the Presence of Dichlorobisphosphinenickel(II), NiL_2Cl_2, as Catalyst.[a]

R in RMgBr	Aryl halide	L_2 in NiL_2Cl_2[b]	Product (yield, %)
Mesityl	Chlorobenzene	dpp	2-Phenylmesitylene (6)
Mesityl	Bromobenzene	dpp	2-Phenylmesitylene (78)
Mesityl	Bromobenzene	dmpe	2-Phenylmesitylene (85)
Mesityl	Bromobenzene	$2Ph_3P$	2-Phenylmesitylene (96)
Mesityl	α-Bromonaphthalene	dpp	α-Mesitylnaphthalene (45)
Mesityl	*o*-Bromoanisole	dpp	*o*-Mesitylanisole (74)
Phenyl	Mesityl bromide	dpp	2-Phenylmesitylene (48)

[a] Reactions were carried out in a similar manner to that described previously (ref. 8); Grignard reagent : aryl halide : catalyst = 1 : 1 : 0.01 (mol). The mixture was refluxed for 20 hr. Yields were determined by glc.

[b] Dpp = 1,2-bis(diphenylphosphino)propane; dmpe = 1,2-bis(dimethylphosphino)ethane.

A novel asymmetric synthesis of biaryl atropisomers is now possible for the first time by the application of this method using nickel catalysts containing a chiral phosphine ligand. Thus, in the presence of [Ni(-)-diopCl_2] [diop = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane][12-14)] (1 mol %) 1-bromo-2-methylnaphthalene was allowed to react with one equivalent of 2-methyl-1-naphthylmagnesium bromide at room temperature for 29 hr. Normal work-up followed by preparative TLC (Silica Gel, hexane) afforded 2,2'-dimethyl-1,1'-binaphthyl, $[\alpha]_D^{27}$ + 0.39° (c 4.6, ethanol), 1.9% optically pure[15)] *S* isomer,[16)] in 32% yield. Better optical yield [$[\alpha]_D^{26}$ +0.96° (c 3.75, ethanol), 4.6% optical purity] was obtained with a nickel catalyst of the recently reported chiral bidentate phosphine, (*S*)-α-[(*R*)-1',2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine.[17)]



ACKNOWLEDGEMENT

Partial support of our work by the Asahi Glass Foundation for the Contribution to Industrial Technology is gratefully acknowledged.

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(Received December 4, 1974)