

NICKEL AND PALLADIUM COMPLEX CATALYZED CROSS-COUPLING REACTIONS OF ORGANOMETALLIC REAGENTS WITH ORGANIC HALIDES

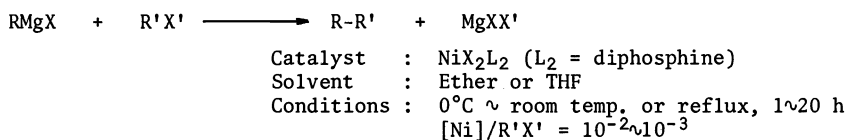
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Abstract — The discovery in 1972 by two research groups that dihalodiphosphenickel(II) complexes exhibit extremely high catalytic activity for selective cross-coupling of Grignard reagents with sp^2 -carbon halides has aroused wide-spread interest in application in organic synthesis of this type and related reactions involving other organometallics than Grignard reagents and not only nickel but also palladium complexes as catalysts. In this lecture several aspects of the title subject will be described centering argument on the Grignard coupling using a variety of phosphine-nickel and -palladium complexes of the formula MCl_2L_2 ($M = Ni$ or Pd ; $L_2 =$ diphosphine) as catalyst precursors.

INTRODUCTION

The coupling of organic halides with organometallic reagents to form the carbon-carbon σ bond is a reaction of tremendous importance in organic synthesis. Although the reaction can be effected in various ways, transition metal salt or complex catalyzed coupling is by far the most esthetic and practical one. The systematic, but largely mechanistic, study of the influence of catalytic amounts of transition metal salts (mostly cobalt(II) chloride) on the interaction of Grignard reagents with organic halides dates from the researches of Kharasch and coworkers (1), but it was not until 1971 - 1972 that such catalytic reactions received much attention owing to their very wide applicability in organic synthesis. In 1971, Tamura and Kochi (2) published the first paper of a series of studies and described that some "soluble catalysts" containing silver, iron, or copper in tetrahydrofuran were extremely effective for coupling of Grignard reagents with organic halides. In 1972, Corriu and Masse (3), and Tamao, Sumitani and Kumada (4) disclosed almost simultaneously a very efficient method for selective carbon-carbon bond formation by nickel complex catalyzed cross-coupling of Grignard reagents with sp^2 -carbon halides.



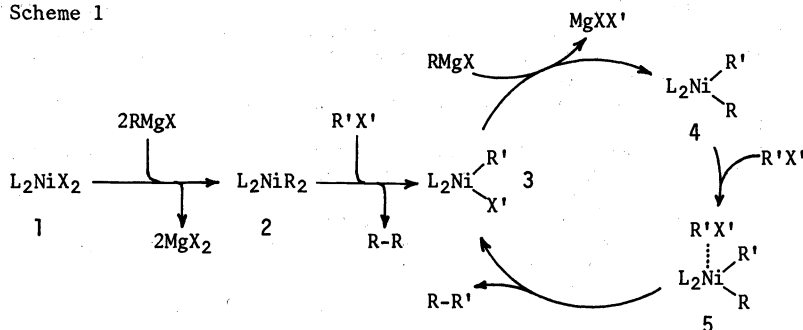
The latter method has aroused wide-spread interest in related reactions as well, which involve other organometallics than Grignard reagents, and not only nickel but also palladium complexes bearing various phosphine ligands (including chiral ones) as catalysts. This lecture will discuss several aspects of the title subject centering argument on our own work (5), with briefly referring to other researchers' work where appropriate, mostly in the last part of the talk.

DESIGN OF A CATALYTIC CYCLE AND SOME REPRESENTATIVE EXAMPLES OF SYNTHESIS

When undertaking this series of studies (4), we designed the catalytic process of the cross-coupling reactions as pictured in Scheme 1 by combining two well-established facts in the chemistry of σ -organonickel complexes bearing "stabilizing" ligand(s): (1) two organic groups on a nickel complex L_2NiR_2 are released by the action of, for example, a halobenzene $R'X'$ to undergo coupling, with the formation of $L_2Ni(R')(X')$ (6), and (2) such a halogen-nickel bond is readily replaced by a Grignard reagent to form the corresponding organonickel bond, $L_2Ni(R')(R)$ (7).

Thus, a dihalodiphosphenickel 1 reacts with a Grignard reagent to form the intermediate diorganonickel complex 2 which is subsequently converted to the halo(organo)nickel complex 3 by an organic halide. Reaction of 3 with the Grignard reagent then forms the new diorgano

Scheme 1



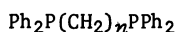
complex 4 from which the cross-coupling product is released by the attack of the organic halide, possibly via the pentacoordinate intermediate 5, and thereby the original complex 3 is regenerated to complete the catalytic cycle.

The reaction, indeed, could be achieved with great success by adding Grignard reagents to a vinylic, aromatic or unsaturated heterocyclic halide in the presence of a catalytic amount of a dihalodiphosphenickel(II) and the yields of products were generally very high.

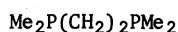
Scheme 1 may be a mere design of the catalysis and not describe the true mechanism of the reaction since an alternative process by Felkin and Corriu and their coworkers (8,9) may be equally possible, who have proposed one involving the oxidative addition of a Grignard reagent to nickel(0) species for a series of nickel-catalyzed Grignard reactions. However, subsequent mechanistic studies by several research groups (2c,5a,10) provide results essentially consistent with Scheme 1 and, moreover, almost all of the reactions that will be described below can be accommodated within this Scheme.

Recently, it has been established by several research groups including ours that a number of analogous palladium complexes PdX_2L_2 and $\text{Pd}(\text{PPh}_3)_4$ not only can be employed as effective catalyst precursors but also, in some cases, have a superiority over the nickel catalysts in catalytic activity, selectivity of product formation, and capability of use of a wide range of organometallics.

For reasons of clarity, we first describe some representative examples of the nickel catalyzed cross-coupling reaction. Diphosphine ligands used for ordinary cross-coupling are given below with their abbreviations. Chiral phosphines for asymmetric cross-coupling will be shown later.



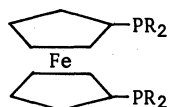
$n = 2$, dppe
 $n = 3$, dppp
 $n = 4$, dppb



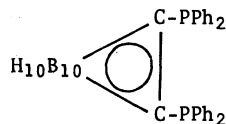
dmpe



cis-dpen

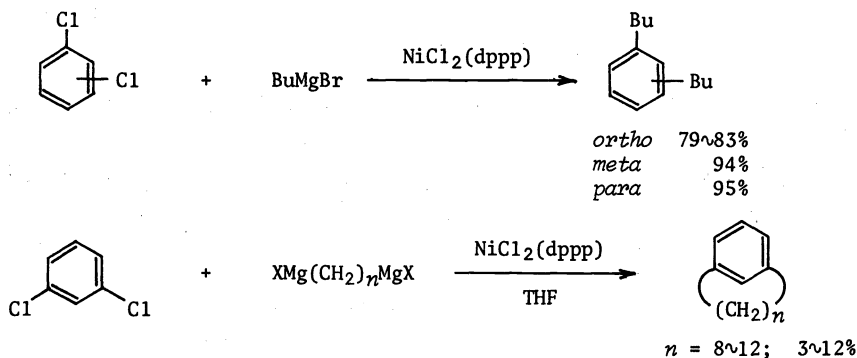


R = Me, dmpf
 R = Ph, dppf



dppc

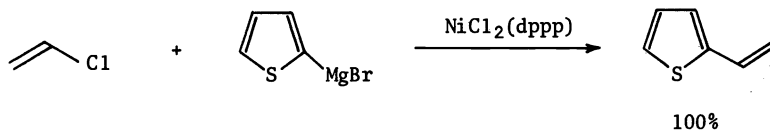
I would like to begin with describing some of the examples which were obtained in our early studies but are among the most characteristic of the title reaction. These are mono- and dialkylation of aromatic mono- and di-halides, respectively, by primary alkyl Grignard reagents in the presence of $\text{NiCl}_2(\text{dppp})$, which proceed without any positional scrambling and alkyl group isomerization, e.g. (4,5b,11,12),



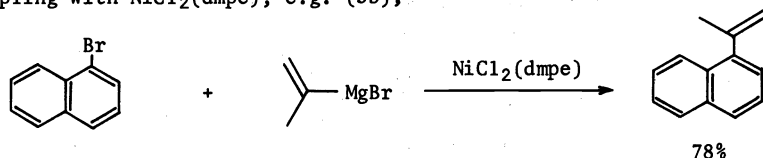
The halides may be chlorides, bromides, or iodides, although chlorides usually give the most satisfactory results. Even fluorides react with comparable facility in some cases. The reactivity of halobenzenes decreases in the order $\text{PhI} > \text{PhBr} > \text{PhCl} > \text{PhF}$. Diethyl ether is, in general, better than THF as solvent.

Some of further examples that represent distinctly the characteristics and utility of the reaction are as follows.

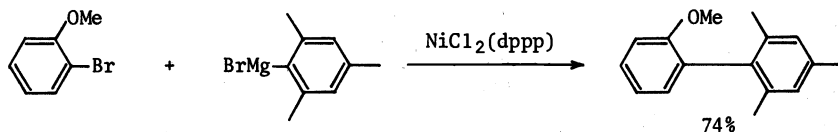
Vinyl chloride is one of the most reactive halides and vinylation of Grignard reagents proceeds very smoothly below room temperature, e.g. (5b,13),



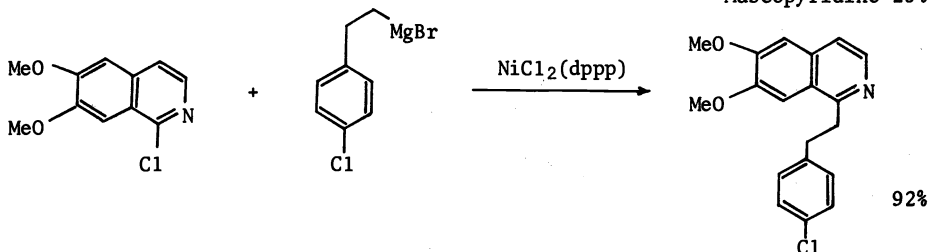
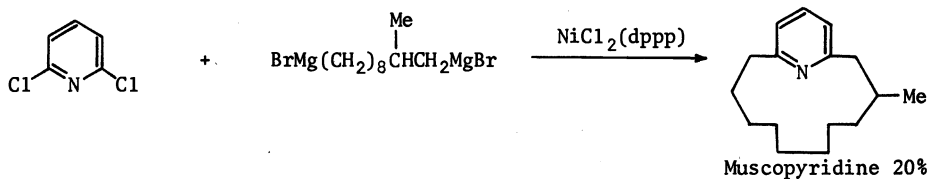
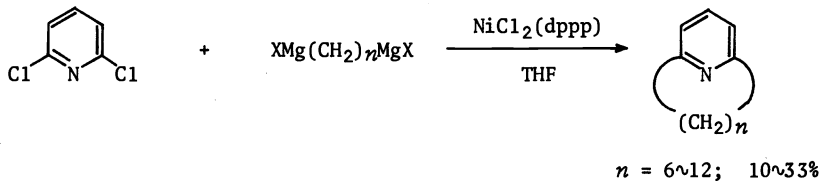
Allyl and alkenyl Grignard reagents are virtually unreactive with $\text{NiCl}_2(\text{dppp})$, but smoothly undergo coupling with $\text{NiCl}_2(\text{dmpe})$, e.g. (5b),



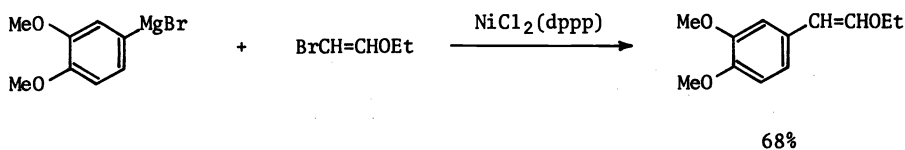
Sterically hindered aryl-aryl coupling is also possible, e.g. (5b,14),

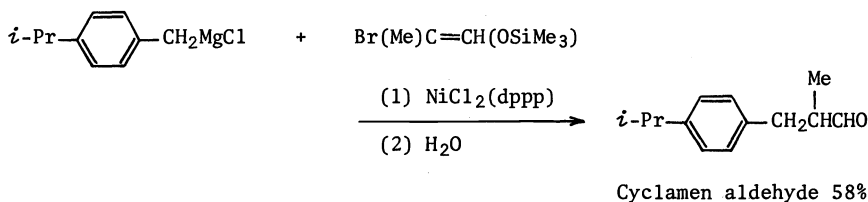


Coupling with unsaturated *N*-containing six-membered ring halides may open up a new, convenient synthetic route to [n](2,6)pyridinophanes and alkaloids (12,13), e.g.,

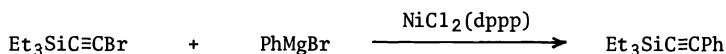


Coupling of α -bromo enol ethers yields homologated enol ethers as exemplified by the following two equations (15).





Haloacetylenes also undergo coupling very easily to give disubstituted acetylenes (16).



Hundreds of compounds, some of which otherwise are not readily accessible, have been prepared very conveniently and in moderate to exceedingly high yields by the present method. They are listed, together with reaction conditions and yields, in our forthcoming review article (17).

CATALYTIC ACTIVITY OF NICKEL-PHOSPHINE COMPLEXES

In the light of the fact that coupling of the *n*-butyl Grignard reagent with chlorobenzene readily goes to completion under suitable conditions, it was chosen as a model reaction for the estimation of the catalytic activity of various phosphine-nickel complexes. The reaction conditions and results are listed in Table 1 (5b).

TABLE 1. Catalytic activity of various NiCl₂L₂


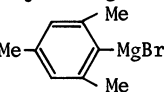
PhCl	+	BuMgBr	$\xrightarrow[\text{Et}_2\text{O, reflux, 20 h}]{\text{NiCl}_2\text{L}_2\text{ (1\%)}}$	Ph-Bu
L ₂				Yield (%) of PhBu
dppp				100
dmpf				94
2Ph ₃ P				84
dppe				79
dmpe				47
dppc				28
dppb				28
<i>cis</i> -dpen				20
2Et ₃ P				6
2Ph ₂ MeP				4
				Not determined

The catalytic activity of the nickel complexes depends strongly upon the nature of the ligands. As might be inferred from Scheme 1, generally speaking, bidentate phosphines as ligands exhibit much higher catalytic activity than unidentate ones; the efficiency of the bidentate phosphine ligands decreases roughly in the sequence: dppp > dmpf > dppe > dmpe > dppc > *cis*-dpen. The prominence of NiCl₂(dppp) as catalyst is common for many other combinations of Grignard reagent and halide as well, as illustrated in the several aforementioned syntheses. However, for the cross-coupling of CH₂=CHCH₂MgBr and CH₃CH=CHMgBr with bromobenzene (Table 2) as well as that of CH₂=C(Me)MgBr with α -bromonaphthalene (*vide supra*), NiCl₂(dmpe) exhibits seemingly unusually high catalytic activity. Of the unidentate phosphines as ligands, only triphenylphosphine is practically active for the coupling. In some reactions involving sterically hindered aryl Grignard reagents such as mesitylmagnesium bromide and bromobenzene, this unidentate phosphine is even better than dppp (Table 2) (5b). Although with NiCl₂(PEt₃)₂ chlorobenzene is consumed significantly, reduction of the halide to benzene is the major reaction (*vide infra*). At the present time we are not in a position to rationalize the marked differences in catalytic activity and selectivity (*vide infra*) which are brought about by the delicate steric and electronic changes in phosphine ligands.

ALKYL GROUP ISOMERIZATION

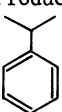
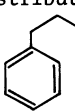

As already illustrated, any primary alkyl Grignard reagent replaces a halogen atom of the organic halide by its primary alkyl group, regardless of the phosphine ligand in the nickel catalyst. On the contrary, the cross-coupling reaction between secondary alkyl Grignard reagents such as *i*-PrMgCl with, say, chlorobenzene has been found to be accompanied by alkyl group isomerization from secondary to primary and reduction of the halide. The product from chlorobenzene, therefore, is in general a mixture of the expected *n*-alkylbenzene, the iso-

TABLE 2. Catalytic activity of NiCl₂L₂ (1%) for the coupling of various Grignard reagents with organic halides

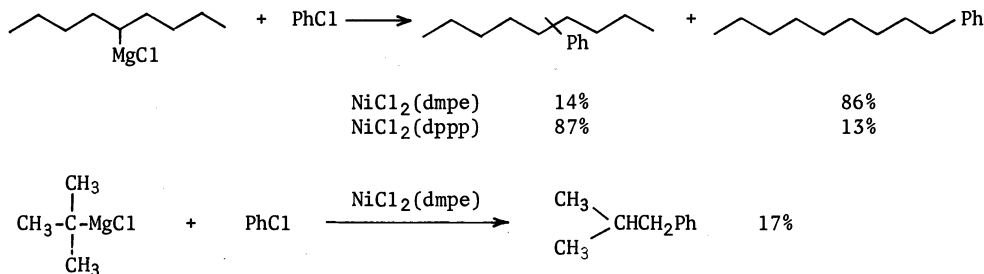
RMgX	Halide	Yield (%) of coupling product				
		L ₂ = dppp	dppe	dmpe	2Ph ₃ P	2Et ₃ P
PrMgBr	PhCl	94	—	19	72	—
<i>i</i> -PrMgCl	PhCl	89	74	81	20	trace
MeMgBr	PhCl	100	65	—	—	—
MeMgBr		98	24	—	—	—
Me ₃ SiCH ₂ MgCl	PhCl	100	0	16	53	95
CH ₂ =CHCH ₂ MgBr	PhBr	trace	trace	63	36	37
CH ₃ CH=CHMgBr	PhBr	16	—	84	15	—
	PhBr	78	—	85	96	—
<i>n</i> -C ₈ H ₁₇ MgCl	CH ₂ =CHCl	—	95	—	72	48
PhMgBr	CH ₂ =CHCl	—	89	—	63	58

merized *sec*-alkylbenzene, and benzene itself. The extent of both isomerization and reduction is dependent strongly upon the electronic nature of the phosphine ligand (18). Table 3 shows the total yields and product distributions from the reaction of *i*-PrMgCl with chlorobenzene in refluxing ether for 20 h in the presence of nickel catalysts containing various phosphine ligands. It is seen that, apart from the total yield, phosphines which give rise to preferential formation of the expected isopropylbenzene are dppe, dppp, dppc, and *cis*-dpen, whilst phosphines which induce the alkyl group isomerization and/or reduction are dmpe, dmpf, and all the unidentate phosphines. These results suggest that, as far as bidentate ligands are concerned, the more electron-donating the phosphine, the greater is the extent of the isomerization.

TABLE 3. Products from the reaction of *i*-PrMgCl with PhCl in the presence of NiCl₂L₂

L ₂ in catalyst	Total yield (%)	Products distribution (%)		
				
dppe	74	96	4	0
dmpe	84	9	84	7
dppp	89	96	4	0
dmpf	48	8	74	18
dmpc	7	12	88	0
dppc	18	78	1	21
<i>cis</i> -dpen	8	92	8	0
2PEt ₃	9	1	11	88
2PBu ₃	8	2	16	82
2PPh ₃	44	16	30	54

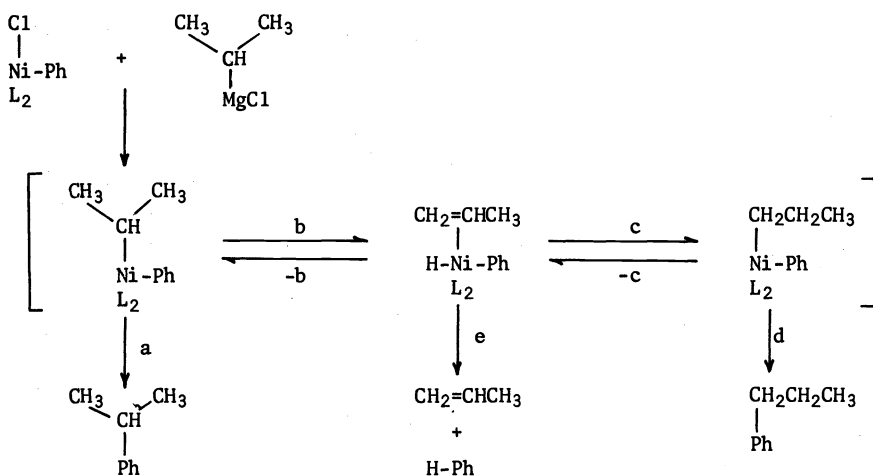
With NiCl₂(dmpe) as catalyst the isomerization readily occurs even along four carbon-carbon single bonds. Tertiary-to-primary isomerization also is induced by this catalyst (19).



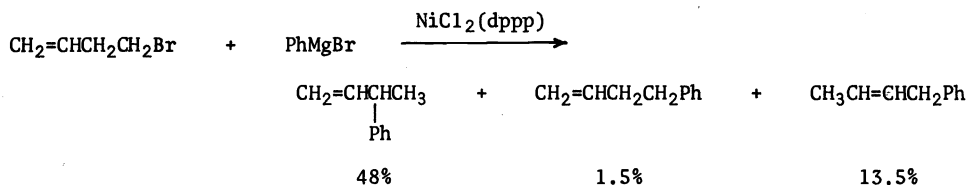
The alkyl group isomerization and reduction processes accompanying the coupling can be best understood in terms of Scheme 2, which involves σ, π -rearrangement between two σ -alkylnickel

intermediates and one hydrido(olefin)nickel intermediate. The electronic effects of the ligand attached to nickel channel the reaction via one of the pathways in preference to the other. An increase in the electron density on nickel owing to the good electron-donating ligands may facilitate the σ - π conversion (step b). This may be understood in the following way. The "8-effect" due to the high electron density on nickel should lower the activation energy for the σ - π conversion (20). Furthermore, the carbon atom σ -bonded to nickel in the "active catalyst" is considered to be more or less carbanionic, and in this sense, the primary alkyl group in the intermediate is favored over the secondary alkyl group. The validity of this Scheme may be supported by the fact that benzene which would arise from the decomposition of the hydrido-olefin intermediate (step e) is formed, with a few exceptions, only in cases where not isopropyl- but *n*-propylbenzene is formed preferentially.

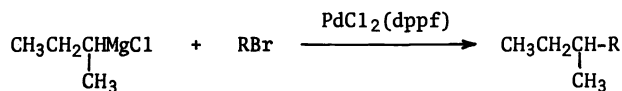
Scheme 2



In connection with the above-mentioned isomerization accompanying the cross-coupling, it seems of interest to note that coupling of 3-butenyl bromide with the phenyl Grignard reagent is accompanied rather extensively by a primary alkenyl-to-secondary alkenyl isomerization with $\text{NiCl}_2(\text{dppp})$ (21).



It is pertinent to remark here on one of the most important recent results in relation to the cross-coupling with secondary alkyl Grignard reagents (22). This is concerned with the reaction of *sec*-butylmagnesium chloride with bromobenzene, β -bromostyrene and 2-bromopropene using $\text{PdCl}_2(\text{dppf})$ as catalyst. In each case, the *sec*-butyl group is transferred as such (with no isomerization) nearly quantitatively to the unsaturated moiety of the halide. A number of palladium catalysts bearing any other ligand gave only poorer results (Table 4). The precise role of the ferrocene moiety in *dppf* yet remains to be clarified.



GEOMETRICAL ISOMERIZATION OF 1-ALKENYL GRIGNARD REAGENTS

The nickel catalyzed Grignard cross-coupling reaction with monohaloolefins takes place stereospecifically with complete retention of geometrical configuration. For instance, *cis*- and *trans*- β -bromostyrene are converted exclusively into *cis*- and *trans*-stilbene, respectively, when treated with PhMgBr . The stereochemistry was invariant with the nature of ligands in the catalyst (23). Similar stereochemistry has been found in the reaction of the same bromides with MeMgBr .

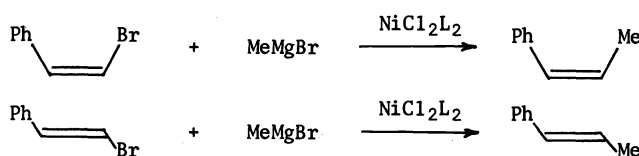
TABLE 4. Cross-coupling of *sec*-butylmagnesium chloride with organic halides catalyzed by palladium complexes

Catalyst	Bromide (RBr)	Reaction conditions		Yield (%) ^a		
		Temp.	Time (h)	<i>sec</i> -BuR	<i>n</i> -BuR	
PdCl ₂ (dppf)	PhBr	r. t.	1	95	0	(0) ^b
Pd(PPh ₃) ₄		r. t.	24	4	6	(31) ^b
PdCl ₂ (PPh ₃) ₂		r. t.	24	5	6	(9) ^b
PdCl ₂ (dppe)		r. t.	48	0	0	(96) ^b
PdCl ₂ (dppp)		r. t.	24	43	19	(23) ^b
PdCl ₂ (dppf)	(<i>E</i>)-PhCH=CHBr ^c	0°C	2	97	0	(0) ^d
Pd(PPh ₃) ₄		0°C	3	33	36	(4) ^d
PdCl ₂ (dppe)		0°C	5	3	3	(38) ^d
PdCl ₂ (dppp)		0°C	5.5	76	5	(6) ^d
PdCl ₂ (dppb)		0°C	3.5	53	25	(8) ^d
PdCl ₂ (dppf)	CH ₂ =CMeBr	0°C	8	80	0	

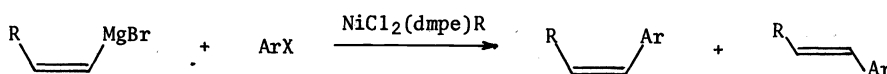
^a Determined by glpc using an internal standard. ^b Recovered bromobenzene (%).

^c The coupling products, *sec*-butyl- and *n*-butylstyrene have *E* configuration (>99%).

^d Yield (%) of styrene.



In striking contrast, the cross-coupling of 1-alkenyl Grignard reagents with aryl halides in the presence of NiCl₂(dmpe) as catalyst is non-stereoselective; *viz.*, alkenyl Grignard reagents undergo *cis/trans* isomerization very readily (Table 5) (24).

TABLE 5. Cross-coupling of 1-alkenyl Grignard reagents with aryl halides catalyzed by [NiCl₂(dmpe)] (1%) in THF at 50°C for 40 h

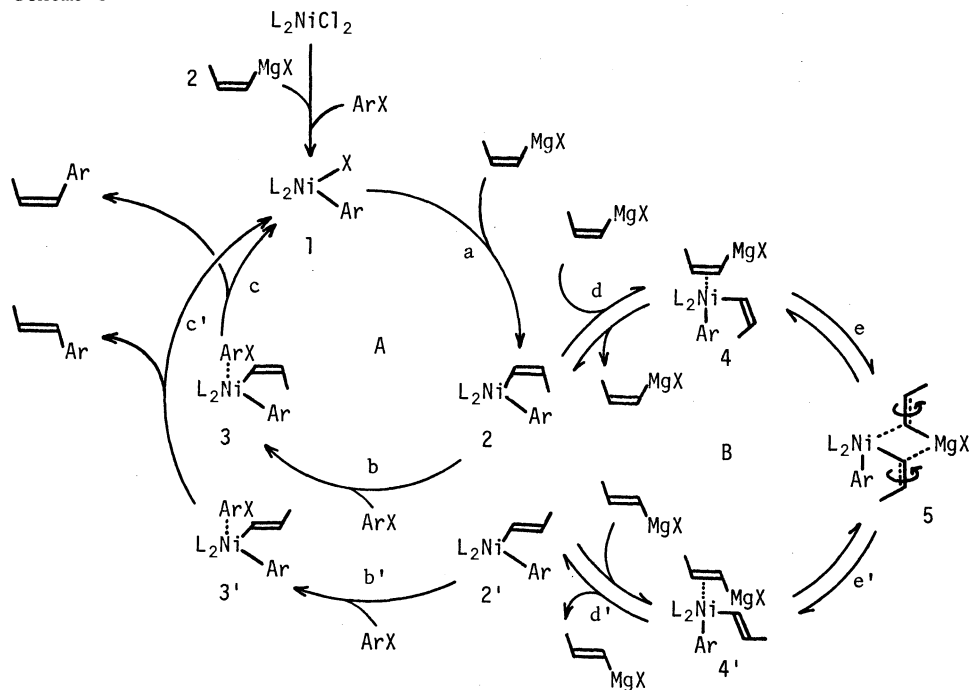
RCH=CHMgBr (A)		ArX (B)	Mole ratio A/B	RCH=CHAr	
R	<i>cis/trans</i>			Yield (%)	<i>cis/trans</i>
Me	96/4	PhCl	1.2/1	15	0/100
Me	96/4	PhBr	1/0.8	84	27/73
Me	96/4	PhBr	1/5	66	73/27
Me	96/4	PhBr	1/20	61	95/5
Me	96/4	4-MeOC ₆ H ₄ Br	1.2/1	79	30/70
Me	96/4	4-ClC ₆ H ₄ Br	1.2/1	95	85/15
Me	96/4	1-NpBr	1.2/1	87	95/5
<i>n</i> -Pr	100/0	PhBr	1.2/1	63	17/83
<i>i</i> -Pr	94/6	PhBr	1.2/1	41	68/32
Ph	71/29	PhBr	1.2/1	42	1/99

The stereochemistry is dependent markedly upon the nature of the aryl halide and the Grignard reagent/halide ratio. Thus the more reactive the aryl halide and the smaller the Grignard/halide ratio, the higher the stereoselectivity.

These results indicate that the low stereoselectivity is attributable to a reaction distinct from, and competitive with, the essentially stereoselective cross-coupling. The observed results can be best understood in terms of Scheme 3. In this Scheme, (halo)(organo)nickel complex 1 reacts with the *cis*-alkenyl Grignard reagent to form *cis*-alkenyl nickel species 2. In cases of reactive and/or an excess of aryl halide being used, 2 may take course (b) to give a *cis*-olefin with retention of configuration via an 18-electron intermediate 3 (cycle A). On the other hand, with an excess of alkenyl Grignard reagent and with less reactive halide, the alkenyl Grignard reagent as an olefinic component may well compete with the aryl halide for coordination with the alkenyl-nickel complex 2 (cycle B). This type of interaction may be responsible for the *cis/trans* isomerization of the alkenyl group(s). Although the nature of this interaction cannot readily be clarified, we suggest the possible intermediacy of species 5, with reference to the known interaction mode between organonickel complexes and aluminum alkyls, proposed by Wilke et al. (7,25) for the so-called "Nickel-Effect". Geometric isomerization around the olefinic bond would be possible in 5, because

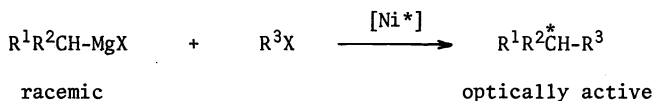
π -bond order would be lowered. The resulting *trans*-alkenyl-nickel species 2' gives a *trans*-olefin when complexed with an aryl halide. An alternative mechanism involving π -allylnickel intermediates has been proposed by Duboudin and Jousseume (26).

Scheme 3

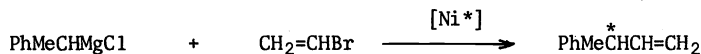


ASYMMETRIC GRIGNARD CROSS-COUPLING

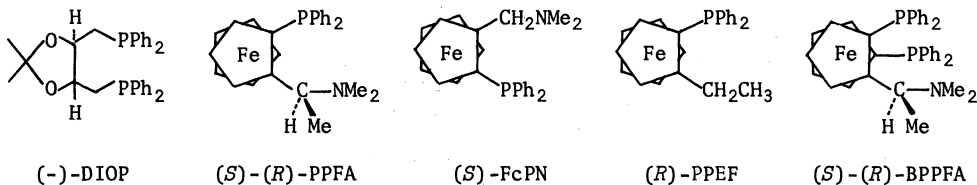
Scheme 1 suggests that the use of chiral phosphine-nickel (or -palladium) complexes as catalysts will provide a new type of asymmetric reactions, giving optically active hydrocarbons. In fact, it was first shown (27,28) that the optically active coupling products could be obtained, although their optical yields were low (7-16%), from the reaction of *sec*-alkyl Grignard reagents with phenyl and vinyl halides using $\text{NiCl}_2[(-)\text{-DIOP}]$ (29) as catalyst. This asymmetric reaction is classified as a kinetic resolution of racemic Grignard reagents.



We have examined in detail the cross-coupling reaction of 1-phenylethylmagnesium chloride with vinyl bromide using the nickel catalyst containing a chiral ferrocenylphosphine, (*S*)-(*R*)-PPFA, (*R*)-(*R*)-PPFA, (*S*)-FcPN, (*R*)-PPEF, or (*S*)-(*R*)-BPPFA (30). (*S*)-(*R*)-PPFA possesses both planar and central elements of chirality, also dimethylamino group on the side chain of



the ferrocene. (*R*)-(*R*)-PPFA is a diastereomeric isomer of (*S*)-(*R*)-PPFA. (*S*)-FcPN lacks the central chirality and (*R*)-PPEF possesses the planar chirality only. These phosphines are expected to permit one to estimate separately the role which each element of chirality and the functionality may play in the present Grignard cross-coupling.



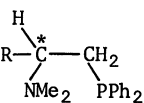
The coupling occurred smoothly at -20 to 0°C within several hours to give optically active 3-phenyl-1-butene in very high chemical yields. Results summarized in Table 6 contain three significant features. Firstly, the coupling product of high optical purity (50-60%) was obtained with PPFA, FcPN, and BPPFA. Although the present asymmetric reaction is a kinetic resolution of the *sec*-alkyl Grignard reagent, the optical purity was not largely affected by the Grignard/halide ratio, indicating that the racemization of the Grignard reagent is fast as compared with the coupling. The high ability of the ligands to cause asymmetric induction is apparent by comparing these results with those obtained with (-)-DIOP (*vide supra*). Secondly, the (*S*)-FcPN ligand, which is analogous to (*R*)-(*S*)-PPFA but has only planar chirality, and (*R*)-(*R*)-PPFA, which has *R* configuration of carbon central chirality as opposed to its epimer (*S*)-(*R*)-PPFA having *S* configuration, showed the asymmetric induction of comparable efficiency to the (*S*)-(*R*)- or (*R*)-(*S*)-PPFA ligand. The result demonstrates that ferrocene planar chirality plays an important role rather than the carbon central chirality. Finally, a dramatic decrease in the asymmetric induction was observed with PPEF as a ligand which contains no dimethylamino group. Thus the dimethylamino group on chiral ferrocenyl-phosphines is the first requisite for the high stereoselectivity in the present asymmetric cross-coupling reaction.

Quite analogous results have been obtained with PdCl₂[(*S*)-(*R*)-BPPFA] catalyst (31).

TABLE 6. Asymmetric cross-coupling PhMeCHMgCl + CH₂=CHBr, catalyzed by chiral nickel complexes

Chiral ligand	Grignard/halide ratio	Reaction temp (°C)	Yield (%)	Optical purity (Configuration)
(<i>R</i>)-(<i>S</i>)-PPFA	4	-20	99	63 (<i>S</i>)
(<i>S</i>)-(<i>R</i>)-PPFA	4	0	99	59 (<i>R</i>)
(<i>S</i>)-(<i>R</i>)-PPFA	2	0	97	56 (<i>R</i>)
(<i>S</i>)-(<i>R</i>)-PPFA	2	0	98	57 (<i>R</i>)
(<i>S</i>)-(<i>R</i>)-PPFA	1	0	83	52 (<i>R</i>)
(<i>R</i>)-(<i>R</i>)-PPFA	2	0	99	50 (<i>R</i>)
(<i>S</i>)-FcPN	4	0	98	60 (<i>S</i>)
(<i>R</i>)-PPEF	4	0	86	4 (<i>S</i>)
(<i>S</i>)-(<i>R</i>)-BPPFA	4	0	73	60 (<i>R</i>)

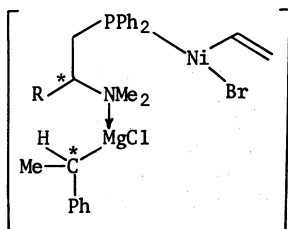
In our recent study (32) of the same asymmetric cross-coupling as mentioned above, exceedingly high optical yields up to 81-94% of the product, 3-phenyl-1-butene, have been obtained (in quantitative chemical yield) with the nickel catalyst containing a chiral β-dimethylamino-alkylphosphine:

		Optical yield of product
	R = Me (<i>S</i>)	(<i>S</i>)-Alaphos 38% e.e. (<i>S</i>)
	R = CH ₂ Ph (<i>S</i>)	(<i>S</i>)-Phephos 71% e.e. (<i>S</i>)
	R = Ph (<i>R</i>)	(<i>R</i>)-PhGlyphos 70% e.e. (<i>R</i>)
	R = <i>i</i> -Pr (<i>S</i>)	(<i>S</i>)-Valphos 81% e.e. (<i>S</i>)
	R = <i>t</i> -Bu (<i>R</i>)	(<i>R</i>)- <i>t</i> -Leuphos 94% e.e. (<i>R</i>)

In marked contrast, (*S*)-2-diphenylphosphinopropyldimethylamine and (*S*)-1,2-bis(diphenylphosphino)propane (33), the structures of which are closely related to those of the aminoalkylphosphines described above, gave rise to only 25 and 0% optical yield, respectively, though the chemical yield of the product was quantitative in both cases.

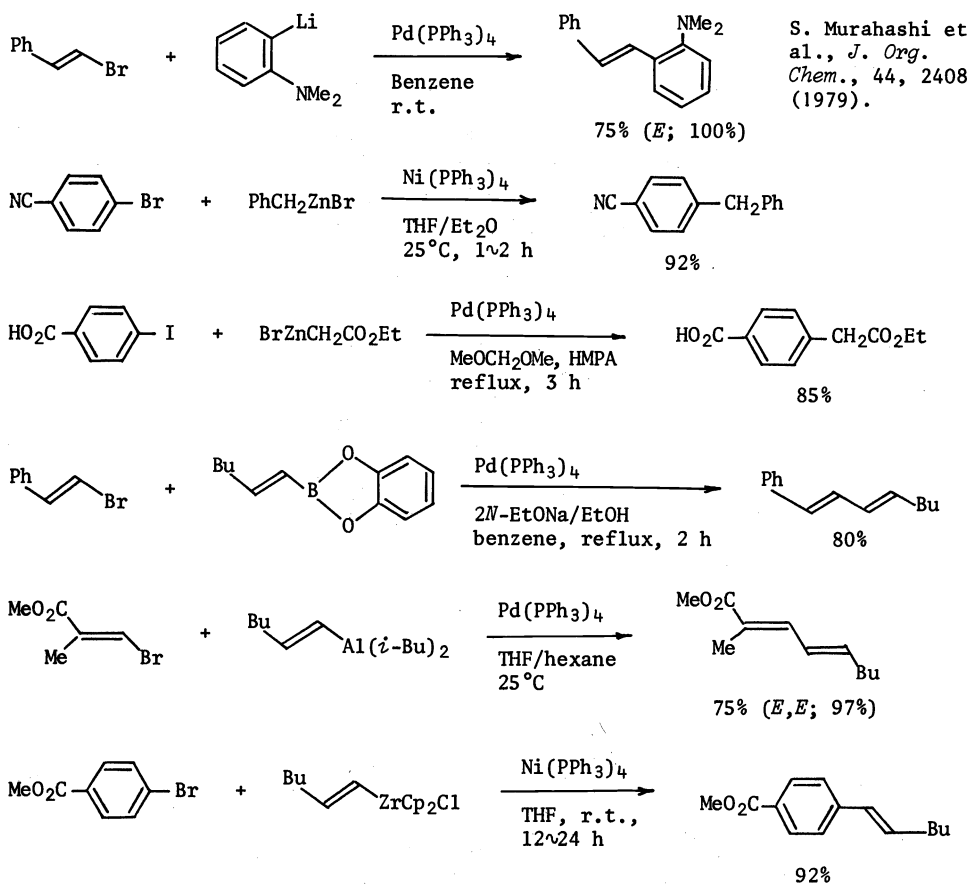


These results clearly indicate, here again, that the presence of the dimethylamino group in the ligands is playing a key role, and seem to be accommodated within Scheme 1. Thus, when the Grignard reagent approaches the "active catalyst" analogous to 3, the Me₂N group in the aminophosphine ligand dissociates from the nickel and coordinates with the magnesium atom in the Grignard reagent to form the diastereomeric transition state or intermediate as shown below. This coordination must occur selectively with one of the enantiomers of the Grignard reagent that, probably, always exists in a racemic form, and the selectivity is affected by the steric bulkiness of the alkyl group at the chiral carbon atom on the ligand. Subsequent attack of the 1-phenylethyl group on the nickel leads to the diorganonickel intermediate. Finally, coupling to form the optically active product may occur by the aid of vinyl bromide with regeneration of the "active catalyst".



CROSS-COUPLING WITH ORGANOMETALLICS OTHER THAN GRIGNARD REAGENTS

Discovery of the phosphine-nickel complex catalyzed cross-coupling of Grignard reagents with organic halides has encouraged subsequent remarkable developments in organic synthesis using a wide range of organometallics besides Grignard reagents and the palladium as well as nickel complexes as catalysts. The organometallic reagents include those of lithium (34), zinc (35), boron (36), aluminum (37), and zirconium (38), and $\text{Pd}(\text{PPh}_3)_4$ has proved to be by far the most suitable of catalyst precursors in many cases where these reagents are employed. Use of a variety of combinations of reagent and catalyst has made it possible to prepare, in good yields and with high selectivity, a vast range of organic compounds, even containing various functional groups, which cannot be accessible by the use of Grignard reagents. Furthermore, it should be noted that many of the organo-boron, -aluminum and -zirconium reagents can be made very conveniently via hydrometalation of carbon-carbon multiple bonds. Only a few representative examples of synthesis are given in the following equations.



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