with the 3 isomer but a trace of the cyclopentadiene dimer. The adduct was methylated to give 2-cyclopentenyltrimethylsilane: bp 99–100°; n^{20}D 1.4485; d^{20}_4 0.8131; $[\alpha]^{20}$D −7.54° (neat).[12,13] Similarly, hydrosilylation of 1,3-cyclohexadiene (25 mmol) with excess trichlorosilane catalyzed by Pd(II)–MDPP gave two isomeric cyclohexenyltrichlorosilanes (9:1 by glpc analysis) (71% yield), which led, upon methylation, to 2-cyclohexenyltrimethylsilane, n^{20}D 1.4629, d^{20}_4 0.8361; $[\alpha]^{20}$D −11.08° (neat),[12] as the major component.

The significant feature of the present results is twofold. First, it will be reasonable to conclude that a catalyst involves the intervention of π-allylic metal intermediates, since the catalytic action of palladium (and nickel) complexes in hydrosilylation of 1,3-dienes distinctly differs from that of platinum for which π-allylic complexes are rather unusual.[14] Furthermore, it has recently been reported that even aromatic ring carbons can be contained in the formation of a π-benzyl complex with palladium.[15] The formation of α-phenylethyltrichlorosilane as a sole product in the palladium complex catalyzed hydrosilylation[16] may be ascribed to the incorporation of a silyl group exclusively into a benzylic position of π-α-methylbenzyl–metal bonding, which in turn must exhibit diastereomeric interactions with the chiral phosphine ligands[17] (partial asymmetric induction, *vide infra*).

A second important feature follows from the first: the effect on stereoselectivity given by variation in configuration at the chiral center C-3 of the menthyl system resulted in the formation of enantiomeric (*S*)-(+)- and (*R*)-(−)-α-phenylethyltrichlorosilane (5.1 and 3.3% ee, respectively). However, this regularity was not observed in 2-cycloalkenylsilane formation.[18] It is difficult at present to ascertain the pattern of addition with respect to stereoselectivity in the product as functions of olefins used and phosphine ligands having multiple chiral centers. Nevertheless, the finding of an asymmetric induction in hydrosilylation of cyclic conjugated dienes has some interesting mechanistic implications.

In the light of current views of the mechanisms of metal-catalyzed hydrosilylation,[19,20] the following processes may be involved: (a) insertion of the palladium center into the silicon–hydrogen bond; (b) addition of the resulting hydridopalladium to the cyclic diene to convert it into a π-alkenyl metal bonding; and (c) transfer of the silicon from the metal center to the π-enyl carbon to give the product. Since cyclic π-enyl–palladium bonding has a local plane of symmetry and cannot induce asymmetry, the last process (c) must involve diastereomeric transition states or intermediates (including catalyst complexes), which control the stereochemical course of the present reaction.

Related experiments in regard to platinum-catalyzed hydrosilylation will be reported elsewhere.

Yoshihisa Kiso, Keiji Yamamoto, Kohei Tamao, Makoto Kumada*
Department of Synthetic Chemistry, Kyoto University
Kyoto 606, Japan
Received February 12, 1972

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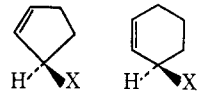

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Selective Carbon–Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickel–Phosphine Complexes

Sir:

We report here a new and useful preparative method of synthesizing unsaturated compounds which involves the selective cross-coupling of a Grignard reagent with a vinyl or aryl halide, *catalyzed* by a nickel–phosphine complex.[1]

The cross-coupling of organic groups by the reaction of Grignard reagents with organic halides is induced by a variety of transition metal halides.[4,5] These reactions are, however, seldom employed in synthetic practice, due to the formation of homo coupling products and a variety of disproportionation products in substantial amounts.

Tamura and Kochi[6] recently demonstrated that "soluble catalysts" consisting of silver, copper, or iron in tetrahydrofuran were extremely effective for the coupling of Grignard reagents with alkyl halides: the first of these was useful for homo coupling and the last two for cross-coupling, especially the iron catalyst, being only for alkenyl halides.[7]

We were primarily interested in two independent facts concerning σ-organonickel complexes. First, two organic groups on a nickel complex are released by the action of an organic halide to undergo coupling, while

(1) It has been reported that dichlorobis(triphenylphosphine)nickel(II) catalyzed the coupling of Grignard reagents with allylic alcohols[2] and hydrosilanes.[3,3a]

(2) C. Chuit, H. Felkin, C. Frajerman, G. Roussi, and G. Swierczewski, *Chem. Commun.*, 1604 (1968).

(3) R. J. P. Corriu and J. P. Masse, *ibid.*, 213 (1970).

(3a) NOTE ADDED IN PROOF. After submission of this paper, a communication (R. J. P. Corriu and J. P. Masse, *Chem. Commun.*, 144 (1972)) dealing with similar cross-coupling reactions to those reported here using nickel catalysts such as Ni(acac)$_2$ reached us.

(4) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, pp 122–137, 1056–1059.

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(7) Although, from the standpoint of the selective cross-coupling of organometallic compounds and organic halides, a π-allylnickel compound and lithium diorganocuprate, first developed by Corey and his group[8,9] and subsequently studied by others,[10] may be cited as excellent reagents, our interest centers on a transition metal *catalyst*.

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(9) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967); **90**, 5615 (1968). This copper method has been extended to the similar reagents containing other metals of the first transition series, involving nickel iodide; see E. J. Corey and G. H. Posner, *Tetrahedron Lett.*, 315 (1970).

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Table I. Nickel–Phosphine Complex Catalyzed Cross-Coupling of Grignard Reagents with Organic Halides[a]

Grignard reagent	Organic halide	Conditions[b]	Product[c]	Yield, %[d]
EtMgBr	PhCl	A	Ph-Et	98[e]
n-BuMgBr	PhCl	A	Ph-*n*-Bu	76
n-BuMgBr	Dichlorobenzene		Di-*n*-butylbenzene	
	o-	A	*o*-	89
	m-	A	*m*-	94
	p-	A	*p*-	95[e]
n-$C_8H_{17}MgCl$	CH_2=CHCl	B	n-$C_8H_{17}CH$=CH_2	95[e]
PhMgBr	CH_2=CHCl[f]	B	PhCH=CH_2	89[e]
PhMgBr	ClCH=CHCl[f]		PhCH=CHPh	
	cis-	A[g]	cis:trans = 80:20	90
	trans-	A	cis:trans = 43:57	81
PhMgBr	Cl_2C=CH_2[f]	A[g]	Ph_2C=CH_2	82
α-NpMgBr[h]	CH_2=CHCl	B	α-NpCH=CH_2	80

[a] The experimental conditions are not necessarily optimum. Grignard reagent/one carbon–halogen bond = 1.1–1.3, [$NiCl_2$(dpe)]/organic halide = 10^{-2}–10^{-3}; solvent is diethyl ether, unless otherwise noted. [b] Condition A is essentially the same as given for *m*-di-*n*-butylbenzene in the text (example 1), and condition B for α-vinylnaphthalene (example 2). [c] Characterized by glpc, nmr, ir, and/or mass spectra. [d] Isolated yields, unless otherwise noted. [e] Yields based on glpc analysis using an internal standard. [f] Reaction proceeded exothermally. [g] In order to ensure the reaction, the mixture was refluxed for 20 hr. [h] Np = naphthyl. Prepared in a mixed solvent of diethyl ether, benzene, and tetrahydrofuran (2:3:1).

the complex itself is converted to the corresponding (halo)(organo)nickel complex,[11,12] as exemplified by eq 1.[11] The second is the well-established fact that such a

$$(\text{dipy})\text{Ni}(\text{Et})_2 + \text{PhCl} \longrightarrow (\text{dipy})\text{Ni}(\text{Ph})(\text{Cl}) \cdot 0.5\text{PhCl} + \text{Et–Et} \quad (1)$$

halogen–nickel bond readily reacts with a Grignard reagent to form the corresponding organonickel bond.[13]

These facts suggest a catalytic ability of a dihalodiphosphinenickel for the coupling of a Grignard reagent with an organic halide.

$$L_2NiX_2 + 2RMgX' \longrightarrow \underset{\mathbf{1}}{L_2NiR_2} + 2MgXX' \quad (2)$$

$$L_2NiR_2 + R'X'' \longrightarrow \underset{\mathbf{2}}{L_2Ni(R')(X'')} + R\text{–}R \quad (3)$$

$$\underset{\mathbf{2}}{L_2Ni(X'')(R')} \overset{RMgX'}{\underset{R\text{—}R'}{\rightleftharpoons}} \underset{\mathbf{3}}{L_2Ni(R)(R')} \overset{MgX'X''}{\underset{R'X''}{\rightleftharpoons}} \quad (4)$$

Thus, a dihalodiphosphinenickel reacts with a Grignard reagent to form the intermediate diorganonickel complex **1** which is subsequently converted to the (halo)(organo)nickel complex **2** by an organic halide. Successive reaction of **2** with the Grignard reagent forms a new diorgano complex **3** from which the cross-coupling product is released by the attack of the organic halide and thereby the original complex **2** is regenerated to complete the catalytic cycle.

The reactions, indeed, can be achieved by the addition of a Grignard reagent to an organic halide in the presence of a catalytic amount of a dihalodiphosphinenickel and the yields are generally very high. Representative results summarized in Table I were observed with dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II), [$NiCl_2$(dpe)].[14] The typical experimental procedures are given for the preparation of hardly accessible *m*-di-*n*-butylbenzene and of α-vinylnaphthalene.

Example 1. To a mixture of [$NiCl_2$(dpe)] (208 mg, 0.39 mmol), *m*-dichlorobenzene (7.93 g, 53.9 mmol), and 50 ml of ether was added *n*-butylmagnesium bromide (120 mmol in 50 ml of ether) at 0° with stirring over 10 min. The resulting black mixture was heated to reflux for 20 hr to form much salt. After hydrolysis with dilute hydrochloric acid, the organic layer and ether extracts from the aqueous layer were combined, washed with water, dried over calcium chloride, and concentrated *in vacuo*. The residue was distilled under reduced pressure to give a colorless liquid (9.63 g, 94%, based on *m*-dichlorobenzene) of pure *m*-di-*n*-butylbenzene: bp 84° (5 mm); n^{20}D 1.4873; lit.[15] bp 75–76° (0.4 mm); n^{25}D 1.4860.

Example 2. Vinyl chloride (6 ml) was condensed at −78° in a 100-ml glass bomb tube containing [$NiCl_2$(dpe)] (178 mg, 0.34 mmol) and 10 ml of ether. To it was added at the same temperature a solution of α-naphthylmagnesium bromide (55 mmol) in 50 ml of a mixed solvent of ether, benzene, and tetrahydrofuran (2:3:1). The bomb was stoppered and allowed to warm up to 0°. The resulting homogeneous solution was then allowed to stand at room temperature for 20 hr. Work-up as above and distillation under reduced pressure afforded 6.8 g (80% based on the Grignard reagent) of α-vinylnaphthalene: bp 89° (5 mm); n^{25}D 1.6418; lit.[16] bp 87° (2 mm); n^{25}D 1.6436.

There are some significant features in this method. (1) A variety of Grignard reagents in ether are applicable and high yields are obtained even from alkylmagnesium reagents containing β-hydrogen atoms.[17] Therefore, the *normal* alkyl derivatives of aromatic compounds, such

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as a series of di-*n*-butylbenzenes which are not readily accessible by conventional methods, can be obtained in one step. (2) Only C_{sp^2} halides, such as vinylic and aromatic, can be used, and especially the high reactivity of *chlorides* offers one of the most remarkable features.[18,19] (3) A bidentate diphosphine as a ligand exhibits the remarkable catalytic activity and the activity decreases in the order[21] $[NiCl_2(dpp)]$[22] > $[NiCl_2(dpe)]$ > $[NiCl_2(dmpe)]$[22] ≈ $[NiCl_2(PPh_3)_2] \gg [NiCl_2(PEt_3)_2] \approx [NiCl_2(PPh_2Me)_2]$. This order suggests that the cis configuration of two organic groups in the diorganonickel intermediate **3** is the first requisite of the catalyst. (4) Both *cis*- and *trans*-1,2-dichloroethylene react with a phenyl Grignard reagent rather nonstereospecifically to give a mixture of *cis*- and *trans*-stilbene anomalously enriched with the cis isomer.[23] (5) Diethyl ether as a solvent is definitely superior to tetrahydrofuran, in contrast with Tamura and Kochi's catalysts.[6]

Further studies are required before the stereochemical and mechanistic details can be understood, apart from the working hypothesis described above.

Investigations are continuing on the extension, refinement, and application of the promising reaction reported here.

(18) Bromides and iodides have been used so far in almost all cases.[6,8-10]

(19) It has been confirmed that the sp^2 carbon–chlorine bond undergoes a reaction of eq 1 type[11,12] and oxidative additions to low valent nickel complexes.[20]

(20) R. Ugo, *Coord. Chem. Rev.*, **3**, 319 (1968); D. R. Fahey, *J. Amer. Chem. Soc.*, **92**, 402 (1970); D. H. Gerlach, A. R. Kane, G. W. Parshall, J. P. Jesson, and E. L. Muetterties, *ibid.*, **93**, 3543 (1971); M. Hidai, T. Kashiwagi, T. Ikeuchi, and Y. Uchida, *J. Organometal. Chem.*, **30**, 279 (1971); see also J. H. Nelson and H. B. Jonassen, *Coord. Chem. Rev.*, **6**, 27 (1971).

(21) This order was observed in the coupling of *n*-butylmagnesium bromide with chlorobenzene.

(22) The ligands dpp and dmpe refer to $Ph_2P(CH_2)_3PPh_2$ and $Me_2PCH_2CH_2PMe_2$, respectively.

(23) This reaction may offer a facile route to *cis*-stilbene.

Kohei Tamao, Koji Sumitani, Makoto Kumada*
Department of Synthetic Chemistry, Kyoto University
Yoshida, Kyoto 606, Japan
Received February 15, 1972

Evidence for the Participation of Aspartic Acid-194 in a New Acylation–Deacylation Reaction of α-Chymotrypsin

Sir:

Circumstantial evidence based on X-ray data suggests that the unusual reactivity of the acyl group acceptor (Ser-195) of α-chymotrypsin (α-CT) would originate from its participation in a proton relay system involving an array of hydrogen bonds between Asp-102, His-57, and Ser-195.[1-4] In addition, a salt bridge between Asp-194 and Ile-16 would somehow favor a precise alignment of these residues with some key parts of substrates.[1-4] In fact, acylation of Ile-16 virtually abolishes activity.[5] However, analogous direct experimental evidence for the precise role of Asp-194 in catalysis is still lacking. We submit experimental observations which offer new perspectives on the elusive role of this acid residue in α-CT catalysis.

The potent depressant[6] and peptide bond forming reagent EEDQ[7] (1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) smoothly transforms carboxyl groups into mixed anhydrides.[7] It also inhibits, sometimes irreversibly, certain serine hydrolases including α-CT.[8] It appears that carboxyl functions act as special "recognition sites" for EEDQ.[7,8] We have confirmed this by comparing the effects of various anions on the acid-catalyzed decomposition of EEDQ to quinoline, CO_2, and ethanol. It can be seen in Figure 1 that in the pH range of 4.5–6.5, acetate is about ten times more efficient than other common anions and thus behaves as a special catalyst of these decomposition reactions. General acid catalysis of the displacement of the 2-ethoxy group by acetate would give an intermediate decomposing irreversibly to a mixed anhydride by a downhill concerted process seemingly unique to carboxyl functions[7] [and perhaps phosphate to some extent (Figure 1)]. The intermediacy of the mixed anhydride when acetate is present was readily confirmed using hydroxylamine as the trapping agent in the usual manner.

When α-CT (0.2 mg/ml in 0.1 *M* NaCl) was exposed at 25° and acid pH to EEDQ at $1-5 \times 10^{-5}$ *M*, inhibition of L-ethyl *N*-acetyltyrosinate hydrolysis (assay at pH 8) built up rapidly, the rate of inhibition appearance being strongly dependent on both EEDQ concentration and pH. Prior addition of proflavin (a known competitive inhibitor of α-CT[9]) at 4×10^{-4} *M* afforded effective protection against EEDQ attack. Typical reciprocal plots for EEDQ inhibition of α-CT at various pH values are shown in Figure 2. Replotting of the appropriate data as in Figure 3 produced a bell-shaped curve[10] whose characteristics allow the following conclusions; the pH_{opt} for inhibition is 5.5 ± 0.2 and two ionizing groups of respective pK_{app} 4.5 ± 0.2 and 6.3 ± 0.2 appear to control the rate. These constants are respectively characteristic of carboxyl and imidazole functions.

At alkaline pH, the EEDQ-inhibited α-CT regenerates swiftly to the extent of 85–90% within 60 min. The pH dependency of this reaction was studied in detail using inhibited α-CT rapidly freed of excess reagent by gel filtration (Sephadex-G25, 0.1 *M* NaCl, 25°, pH 5.5). The results are summarized in Figure 4 where the pH dependency of the regeneration step for the ethoxycarbonyl Ser-195 derivative[11] (prepared from *p*-nitrophenyl ethylcarbonate and α-CT according to the literature[12]) as well as that of ethoxycarbonylimidazole hydrolysis have been included. A pH dependency similar to that of ethoxycarbonylimidazole may be expected for the hydrolysis of a mixed anhydride.[13]

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(10) The curve in Figure 3 need not be corrected for reactivation because in the relevant range of pH values (4.5–6.5), the rates of inhibition are 100–200 times greater than the rates of reactivation.

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