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THE CROSS-COUPLING OF ARYL HALIDES WITH GRIGNARD REAGENTS CATALYZED BY IODO(PHENYL)BIS(TRIPHENYLPHOSPHINE)-PALLADIUM(II) *

AKIRA SEKIYA and NOBUO ISHIKAWA *
Department of Chemical Engineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152 (Japan)

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Summary

The palladium-catalyzed cross-coupling of aryl halides with Grignard reagents affords a variety of biaryls and alkylbenzenes. Based on the proposed catalytic cycle, the complex $(PPh_3)_2Pd(Ph)I$ was found to be a convenient and general catalyst. Certain features of cross-coupling with this catalyst are described.

The formation of carbon—carbon bonds is one of the most important operations in organic synthesis. Transition metal complexes (M) have been shown to be particularly effective catalysts for the coupling [1—6] of organic halides (R′—X) with Grignard or organolithium compounds (R—m) or with potassium cyanide.

$$R{-}m + R'{-}X \xrightarrow{(M)} R{-}R' + m{-}X$$

We have recently described the palladium-catalyzed cyanation [5] of aryl iodides with potassium cyanide using $Pd(PPh_3)_4$ (I) or $(PPh_3)_2Pd(Ph)I$ (II) as catalysts. A recent paper [6] describing the ability of complex I to catalyze a number of cross-couplings between vinyl halides and Grignard reagents prompts us to disclose our own results of a related study which is concerned with the palladium-catalyzed cross-coupling reaction between aryl halides and organo-magnesium and -lithium compounds.

We first found that iodobenzene reacts with phenylmagnesium bromide in the presence of a catalytic amount of complex II to give biphenyl in good yield. Both tetrahydrofuran (THF) and diethyl ether are good solvents for this cross-coupling reaction; this is in marked contrast to the palladium-catalyzed cyanation [5] of

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aryl iodides, in which the use of diethyl ether as solvent gave unsatisfactory results.

Decreasing the quantities of catalyst to even 0.0001 molar equivalent resulted in no appreciable change of the yield of biphenyl (76—82%), indicating the high catalytic ability of the catalyst.

$$\mathrm{PhI} + \mathrm{PhMgBr} \xrightarrow[\text{catalyst}]{(\mathrm{PPh_3})_2\mathrm{Pd(Ph)I}\ (\mathrm{II})} \mathrm{Ph{-}Ph} + \mathrm{MgBrI}$$

As shown in Table 1, the yields of biphenyl from halobenzenes under the same conditions decreased markedly in the order PhI > PhBr >> PhCl. However, bromobenzene gave biphenyl in good yield (75%) when the reaction was continued for a longer period.

In order to demonstrate the formation of unsymmetrical biphenyls by cross-coupling, experiments were carried out in which *p*-fluorophenylmagnesium bromide was allowed to react with iodobenzene and, alternatively, phenylmagnesium bromide with *p*-fluoroiodobenzene, using II and $(\mathrm{PPh_3})_2\mathrm{Pd}(p\text{-}\mathrm{FC_6H_4})\mathrm{I}$ (III) as catalysts, respectively. In these reactions 4-fluorobiphenyl was obtained in comparably good yields (82—77%) and formation of homocoupling products could not be detected (see run 9 and 10 in Table 2).

In consideration of the catalytic cycle of the above cross-coupling, it is possible to deduce the complex $(\mathrm{PPh_3})_2\mathrm{Pd}(p\text{-}\mathrm{FC_6H_4})\mathrm{Ph}$ (IV) as an intermediate, since the corresponding triethylphosphine complex, $(\mathrm{PEt_3})_2\mathrm{Pd(Ar)Br}$, has been reported [7] to give $(\mathrm{PEt_3})_2\mathrm{Pd(Ar)Ar'}$ [Ar, Ar$'$ = p-$\mathrm{FC_6H_4}$ or Ph(Ar $\neq$ Ar$'$)] when treated with Ar$'$MgBr in benzene/diethyl ether. An attempt to carry out the reaction of III with an equimolar quantity of phenylmagnesium bromide under the same conditions did not result in formation of complex IV, but instead, rapid deposition of palladium metal with simultaneous formation of 4-fluorobiphenyl was observed, presumably owing to the instability of complex IV.

TABLE 1

THE PALLADIUM-CATALYZED COUPLING REACTION [a] OF HALOBENZENES WITH PHENYLMAGNESIUM BROMIDE

Catalyst [b]	Molar equiv.	PhX	Yield [c] (%)
—	—	PhI	5
$\mathrm{L_2Pd(Ph)I}$	1/100	PhI	70
$\mathrm{L_2Pd(Ph)I}$	1/1000	PhI	82
$\mathrm{L_2Pd(Ph)I}$	1/10000	PhI	76
$\mathrm{L_2Pd(Ph)Br}$	1/100	PhBr	44
$\mathrm{L_2Pd(Ph)I}$	1/100	PhCl	5
$\mathrm{L_2Pd(Ph)I}$	1/100	PhBr	75 [d]
$\mathrm{PdL_4}$	1/50	PhI	68
$\mathrm{PdL_4}$	1/50	PhBr	36
$\mathrm{PdL_4}$	1/50	PhCl	2
$\mathrm{PdL_4}$	1/50	PhBr	70 [d]

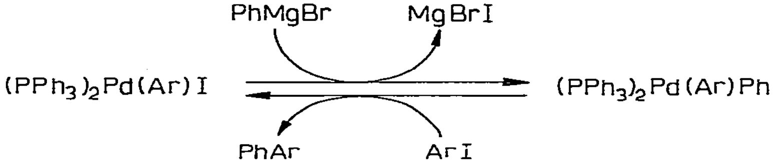
[a] Molar ratio of halobenzene (50 mmol)/phenylmagnesium bromide = 1. Carried out in refluxing THF (55 ml) for 30 min. [b] L = $\mathrm{PPh_3}$. [c] Determined by GLC analysis. [d] Reaction time: 70 min.

$$\underset{\text{(III)}}{(PPh_3)_2Pd(p\text{-}FC_6H_4)I} + PhMgBr \rightarrow \underset{\text{(IV)}}{[(PPh_3)_2Pd(p\text{-}FC_6H_4)Ph]} + MgBrI$$

$$\text{(IV)} \rightarrow Pd + 2\ PPh_3 + p\text{-}FC_6H_4Ph$$

When the reaction was carried out in the presence of an equimolar amount of *p*-fluoroiodobenzene, complex III was regenerated without deposition of palladium metal and 4-fluorobiphenyl was formed. This process is presumed to involve the oxidative addition of *p*-fluoroiodobenzene to a zerovalent palladium species. Therefore, the catalytic role of the palladium complex in the foregoing cross-coupling reaction * which yields 4-fluorobiphenyl is suggested to involve a series of two-electron oxidation and reduction cycles. This leads us to propose Scheme 1 for the palladium-catalyzed cross-coupling reaction, which is similar to the scheme proposed previously for the nickel-catalyzed process [1b].

SCHEME 1



Scheme 1 suggests that not only complex II but also I can function as catalyst, because these complexes are able to transform into $(PPh_3)_2Pd(Ar)I$ in the course of the reaction. Complexes I and II, as catalysts, gave cross-coupling products in yields similar to those obtained with $(PPh_3)_2Pd(Ar)I$ (see Table 1). The use of the latter was most convenient for general and practical purposes, because this is stable enough to be stored without any appreciable change.

Cross-coupling then was examined extensively in the reaction of aryl halides with a variety of Grignard and lithium compounds, using a catalytic amount (0.01 molar equiv.) of complex II. As shown in Table 2, the palladium-catalyzed cross-coupling reaction proves to be useful for the synthesis of various types of substituted benzenes.

This reaction exhibits the following features:

1. *p*-Bromochlorobenzene was coupled, even with a large excess of phenylmagnesium bromide, selectively at the bromine-bound carbon atom to give 4-chlorobiphenyl. The nickel-catalyzed reaction [1], which is known to affect also chlorine substituents on a benzene ring, does not seem to provide such a selectivity.
2. Phenylethynylmagnesium bromide reacted smoothly with iodobenzene to give diphenylacetylene. The nickel-catalyzed reaction [1] is not able to proceed in this way because the coordination of acetylenic compounds to the nickel atom [8] reduces its ability to undergo oxidative addition.
3. Even a sterically hindered compound such as mesitylmagnesium bromide gave a fair yield of the cross-coupling product.

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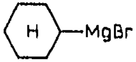
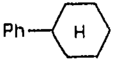
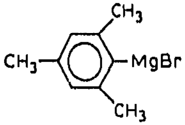
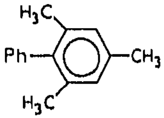
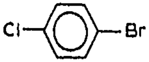
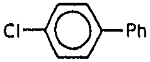
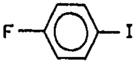
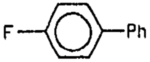
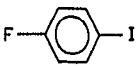
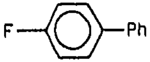
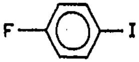
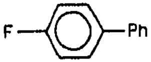
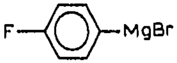
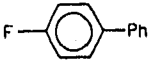
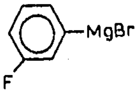
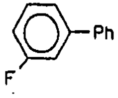
* THF was used as solvent in this reaction but could be replaced by benzene/diethyl ether, in which case the yield was 44%.

TABLE 2

THE PALLADIUM-CATALYZED CROSS COUPLING REACTIONS [a]

Run No.	ArX	R—M (M = MgX or Li)	Catalyst [b]	Product	Bp.(°C/mmHg) (Mp.(°C))		Yield [c] (%)
					This work	Lit.	
1	PhI	PhC≡CMgBr	$L_2Pd(Ph)I$	PhC≡CPh	(59–60.5)	(60–62) [11]	84
2	PhI		$L_2Pd(Ph)I$		156–157/91	239/745 [11]	51
3	PhI	EtMgBr	$L_2Pd(Ph)I$	EtPh	120–125	136.2 [11]	32
4	PhI	n-BuLi	$L_2Pd(Ph)I$	n-BuPh	112–114/38	159.2 [11]	45
5	PhI		$L_2Pd(Ph)I$		150–152/24	276–8.5/746 [12]	64
6		PhMgBr [d]	$L_2Pd(Ph)I$		(73–74)	(77.5) [11]	73 [e]
7		PhMgBr	PdL_4		(72–73)	(74–75) [10]	66
8		PhMgBr	$L_2Pd(Ph)I$		(73–73.5)	(74–75) [10]	74
9		PhMgBr	$L_2Pd(p\text{-}FC_6H_4)I$		(73–74)	(74–75) [10]	82
10	PhI		$L_2Pd(Ph)I$		(72–73)	(74–75) [10]	77
11	PhI		$L_2Pd(Ph)I$		153–154/50	(26–27) [10]	80

[a] THF (55 ml) solution of aryl halide (50 mmol), organomagnesium or lithium compound, and catalyst in 1 : 1 : 0.01 molar proportion was refluxed for 30 min. [b] L = PPh_3. [c] Based on the product actually isolated. [d] Two molar equiv. was used. [e] Reaction time: 70 min.

Experimental

General procedure of the cross-coupling reactions

The experiments shown in Table 2 were carried out by the following general procedure. The palladium catalyst (0.5 mmol) indicated in Table 2 was added to a solution of aryl iodide (50 mmol) in THF (10 ml). To this mixture a Grignard solution, prepared in the usual way from an alkyl or aryl halide (50 mmol) and magnesium foil (55 mg-atom) in THF (45 ml), was added dropwise under reflux. The reaction mixture became clear, and then magnesium salts were deposited. The reaction was exothermic and was generally completed within ca. 30 min. After filtration of the reaction mixture, the filtrate was evaporated and the residue was extracted with hexane to remove the insoluble material. Evaporation of the hexane extracts gave the alkylated or arylated benzene, which was purified by distillation or recrystallization. The reaction with n-butyllithium was carried out similarly to the above procedure, a hexane solution of butyllithium (1.8 *M*) being added to the iodobenzene solution in THF (30 ml).

Yields of the products are listed in Table 2.

Iodo(p-fluorophenyl)bis(triphenylphosphine)palladium(II) (III)

This complex was perpared in 98% yield from *p*-fluoroiodobenzene (6 mmol) and $Pd(PPh_3)_4$ (6 mmol) following the literature procedure [9]. The white crystals decomposed at 182°C. NMR (in C_6D_6): ^{19}F (from int. PhF), —11.4 ppm (m), ^{31}P (from int. PPh_3), —28.8 ppm. (Found: C, 59.7; H, 4.13; F, 2.2. $C_{42}H_{34}FIP_2Pd$ calcd.: C, 59.2; H, 4.02; F, 2.2%.)

Reaction of p-fluoroiodobenzene with phenylmagnesium bromide

(a) A solution of phenylmagnesium bromide prepared from magnesium foil (5.5 mg-atom) and bromobenzene (5.0 mmol) in ether (4.5 ml) was added to a solution of complex III (5 mmol) in benzene (80 ml) at room temperature under nitrogen atmosphere. The solution immediately turned black and palladium metal deposited. After filtration, the filtrate was evaporated to dryness, and the residue was extracted with pentane (150 ml) to remove the insoluble palladium metal and magnesium salts. Evaporation of the pentane solution gave crystals of 4-fluorobiphenyl; mp 72—73°C (lit. [10] 74—75°C), in 80% yield.

(b) The reaction in (a) was carried out in a modified way, where *p*-fluoroiodobenzene (5 mmol) also was dissolved in the benzene solution of complex III. On addition of phenylmagnesium bromide to the benzene solution, no palladium metal precipitated. GLC analysis of the reaction mixture using tetralin as an internal standard showed formation of 4-fluorobiphenyl (54%) and a 36% recovery of 4-fluoroiodobenzene. The reaction mixture was concentrated at room temperature under reduced pressure. The solid was collected by filtration, washed with water, ethanol and ether, and dried to give complex III (dec. 183°C) in 96% yield.

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