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PALLADIUM METAL-CATALYZED CROSS-COUPLING OF ARYL IODIDES WITH ARYLMAGNESIUM BROMIDES. SYNTHESIS OF FLUOROBIPHENYLS*

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Summary

Palladium metal functions as catalyst in the coupling of iodobenzene with phenylmagnesium bromide. For practical purposes, palladium(II) chloride was used instead, since it is converted to palladium metal during the course of the reaction. A high catalytic effect of palladium(II) chloride at low concentrations (saturated solutions in tetrahydrofuran, <0.0001 molar equiv.) was exhibited in cross-couplings yielding several fluorobiphenyls.

Introduction

The coupling reactions between Grignard reagents and aryl or alkyl halides are catalytically induced by several transition metal complexes [1] and halides [2]. The role of the transition metal complexes is known to involve oxidative additon of aryl and alkyl halides to complexes of low oxidation state in the catalytic cycles [3]. On the palladium-catalyzed cross-coupling, reactions have been reported to be catalyzed by triphenylphosphine complexes such as $Pd(PPh_3)_4$ [4, 5], $Pd(Ar)I(PPh_3)_2$ [5] and $Pd(Ph)I(PPh_3)_2$ [5].

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$$\text{Ar-X} + \text{Ar'-X} \longrightarrow \text{Ar-Ar'} \qquad (\text{M} = \text{MgX or Li})$$

Palladium black also is known to function as catalyst in the reactions of aryl halides, for example, in the arylation of olefins [6], and in carboalkoxylation [7,8], amidation [8] and formylation [8] reactions.

Taking these facts into account, we have found a high catalytic efficiency of palladium black in biphenyl formation by the reaction of iodobenzene with phenylmagnesium bromide. Furthermore, we have found that palladium(II) chloride, which is convertible into palladium metal in the course of the reaction, is a more convenient catalyst for this reaction from the practical point of view. The preparation of several fluorobiphenyls was accomplished by this new cross-coupling procedure.

Results and Discussion

In the presence of 0.02 molar equivalent of palladium black, iodobenzene reacted rapidly with phenylmagnesium bromide in refluxing tetrahydrofuran (THF) to give biphenyl in 92% yield. Palladium(II) chloride could be used in place of palladium balck, affording biphenyl in a yield of 88%. In the latter case, the actual catalyst must be palladium metal, the deposition of which was observed at the initial stages of the reaction. The reduction of palladium(II) chloride to palladium metal according to the following equation was confirmed experimentally.

$$\text{PdCl}_2 + 2\ \text{PhMgBr} \longrightarrow \text{Pd} + \text{Ph-Ph} + \text{MgBr}_2 + \text{MgCl}_2$$

As shown in Table 1, THF was found to be the most suitable solvent for this palladium-catalyzed coupling. The use of diethyl ether or a benzene/diethyl ether mixture

Table 1

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

Catalyst	Solvent	Yield[b] of biphenyl (%)
Pd-black	THF	92
$PdCl_2$	THF	88
$PdCl_2$	Et_2O	41[c]
$PdCl_2$	C_6H_6/Et_2O (4:1)	47[c]
$PdCl_2$ + 2 PPh_3	THF	90
$PdBr_2$ + 2 PPh_3	THF	96
$Pd(PPh_3)_4$	THF	68[d]
$Pd(Ph)I(PPh_3)_2$	THF	70[d]

a) Iodobenzene (50 mmol), phenylmagnesium bromide, and catalyst were used in 1 : 1 : 0.02 molar ratio. The reaction was carried out in refluxing solvent (55 ml) for 30 min., except c) under nitrogen.

b) Determined by GLC analysis.

c) Reacted for 60 min.

d) Cited in our previous paper [5].

yields obtained when several other palladium complexes were used (Table 1) indicate sufficiently the high catalytic abilities of palladium black and palladium(II) chloride.

The catalytic efficiency of palladium(II) chloride was surprising. Decreasing the quantity of palladium(II) chloride

Table 2

PREPARATION OF FLUOROBIPHENYLS[a]

ArI	Ar'MgBr	Product	Bp. (°C/mmHg) (Mp. (°C))		Yield[b]
			This work	Lit. [11]	(%)
PhI	p-FC_6H_4MgBr	Ph-C_6H_4F(P)	(73-75)	(74-75)	80 (77[d])
p-FC_6H_4I	PhMgBr	Ph-C_6H_4F(p)	(73-75)	(74-75)	92 (74[d])
PhI	m-FC_6H_4MgBr	Ph-C_6H_4F(m)	135-138/30	(26-27)	87 (80[d])
m-FC_6H_4I	PhMgBr	Ph-C_6H_4F(m)	149-152/48	(26-27)	85 (84)
o-FC_6H_4I	PhMgBr	Ph-C_6H_4F(o)			1[c] (34)

a) A THF (23 ml) solution of aryl halide (25 mmol), arylmagnesium bromide and catalyst in 1 : 1 : <0.001 molar ratio was reflux for 30 min under nitrogen.

b) Based on the product actually isolated unless otherwise noted. Values in parenteses are the yields obtained using $Pd(Ph)I(PPh_3)_2$ (0.01 molar equiv.) as catalyst.

c) Determined by ^{19}F NMR analysis.

d) Cited in our previous paper [5].

yield of biphenyl (95%). Furthermore, even when palladium (II) chloride was used as saturated solution (<0.0001 molar equiv.) in THF, a homogeneous reaction proceeded rapidly and gave the same excellent yield.

Among halobenzenes iodobenzene was exceedingly reactive. When iodo-, bromo-, chloro- and fluorobenzenes were coupled with phenylmagnesium bromide using 0.001 molar equivalent of palladium(II) chloride, yields of biphenyl were 92, 11, 2 and 2%, respectively. The strikingly low reactivity of bromobenzene is in marked contrast to that (75% yield) in the coupling catalyzed by $Pd(Ph)I(PPh_3)_2$ [5].

Cross-coupling was successfully demonstrated by the formation of 3- and 4-fluorobiphenyls in high yield from the corresponding fluoroiodobenzene and phenylmagnesium bromide and, alternatively, from iodobenzene and the appropriate fluorophenylmagnesium bromide, as shown in Table 2. These reactions proceeded rapidly even when very low concentrations of palladium(II) chloride (saturated THF solution) were used. Higher yields of these fluorobiphenyls were realized by this method than by the previously reported procedure using $Pd(Ph)I(PPh_3)_2$ [5]. 2-Fluorobiphenyl, however, could not be obtained by the reaction between o-fluoroiodobenzene and phenylmagnesium bromide (Table 2). This must be due to the fact that a Grignard exchange reaction, followed by benzyne-forming decomposition [9] of the resultant o-fluorophenylmagnesium bromide, proceeds faster than the cross-coupling reaction. An experiment using $Pd(Ph)I(PPh_3)_2$ (0.01 molar equiv.) as catalyst, however, resulted in the formation of 2-fluorobiphenyl and 2,2'-difluorobiphenyl, but only in poor yields (34 and 9%, respectively), presumably because of the rapidity of the cross-coupling.

Further experiments were carried out by allowing 3,5-

difluoroiodobenzene to react with phenylmagnesium bromide and, alternatively, iodobenzene with 3,5-difluorophenylmagnesium bromide in THF saturated with palladium(II) chloride. Both reactions gave considerable amounts of homo-coupling products, 3,3',5,5'-tetrafluorobiphenyl and biphenyl, in addition to cross-coupled 3,5-difluorobiphenyl, in the molar proportions shown below.

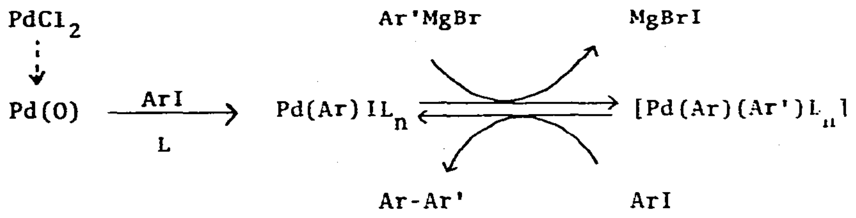
				$3,5\text{-}F_2C_6H_3\text{-}Ph$		$(3,5\text{-}F_2C_6H_3)_2$		Ph_2
$3,5\text{-}F_2C_6H_3I$	+	PhMgBr	$\longrightarrow$	1.00	:	0.24	:	0.23
PhI	+	$3,5\text{-}F_2C_6H_3MgBr$	$\longrightarrow$	1.00	:	0.18	:	0.12

The homo-coupling in these cases must be also due to a rather rapid Grignard exchange reaction, which is promoted by the two electron-withdrawing m-F substituents.

$$3,5\text{-}F_2C_6H_3I + PhMgBr \rightleftharpoons 3,5\text{-}F_2C_6H_3MgBr + PhI$$

In order to confirm this equilibrium, 3,5-difluoroiodobenzene was allowed to react with phenylmagnesium bromide in the absence of catalyst. In this experiment we found the exchange reaction to occur very rapidly. The reaction was followed by ^{19}F NMR measurements, and 75, 85 and 89% conversions of 3,5-difluoroiodobenzene to 3,5-difluorophenylmagnesium bromide were observed in reaction times of 10, 30, and 300 min, respectively.

The high catalytic efficiency of palladium(II) chloride in such extremely low concentrations is presumed to be due to the formation of palladium(0) in the colloidal state at the initial stages of the reaction. In the cross-coupling step, we suggest that an oxidative additon of the aryl iodide to palladium metal [10], presumably with the aid of solvation by THF, takes place, and that the resulting soluble complex begins a catalytic reduction-oxidation cycle, similar to the one previously reported for the $Pd(Ph)I(PPh_3)_2$ catalyzed reaction [5].



L : Solvent

Experimental

General procedure of the cross-coupling reactions

The experiments shown in Table 2 were carried out by the following general procedure. The aryl iodide (25 mmol) was added to a THF solution (5 ml) saturated with palladium(II) chloride (0.0025 mmol) and the whole was warmed. To this solution a Grignard reagent, prepared in the usual way from an aryl bromide (25 mmol) and magnesium foil (27.5 mg-atom) in THF (23 ml), was added dropwise under nitrogen. An exothermic reaction occurred with deposition of magnesium salts. After a 30 min reflux period, the reaction mixture was filtered and evaporated. The residue was extracted with hexane to remove insoluble material. Evaporation of the hexane extract gave the fluorobiphenyl, which was purified by distillation or recrystallization. The products were identified by their IR and ^{19}F NMR spectra, as well as melting points. Yields of the products are listed in Table 2.

Reaction of 3,5-difluoroiodobenzene with phenylmagnesium bromide and that of iodobenzene with 3,5-difluorophenylmagnesium bromide were carried out in the same way as oily products were composed of three materials: 3,5-difluorobiphenyl(I), 3,3',5,5'-tetrafluorobiphenyl(II) and biphenyl (III). Yields of these products were determined by GLC analysis (for III) or by ^{19}F NMR analysis (for I and II) using internal standards. The molar proportions of the products (I), (II), and (III) were as shown above and they were separated by preparative GLC. (I): Liquid; MS, m/e 190 (M^+); ^{19}F NMR (hexane)(from ext. CF_3CO_2H) δ 32.7 ppm t, J_{H-F}^{ortho} 8.5 Hz); (II): m.p. 83-84°C (lit. [12], 85-86°C); MS, m/e 226 (M^+); ^{19}F NMR δ 31.7 ppm (t, J_{H-F}^{ortho} 7.6 Hz) (lit. [12], δ 31.8 ppm, J_{H-F}^{ortho} 7.7 Hz); (III): m.p. 68-69°C (lit. [13], 70.5°C).

Reaction of palladium(II) chloride with phenylmagnesium bromide

A solution of phenylmagnesium bromide, prepared from bromobenzene (30 mmol) and magnesium foil (33 mg-atom) in THF (27 ml), was added dropwise to a mixture of palladium (II) chloride (15 mmol) suspended in refluxing THF (5 ml) under nitrogen. An exothermic reaction occurred and palladium metal rapidly precipitated out. Biphenyl (9 mmol) was detected in the reaction mixture by GLC and the amount was determined by using tetralin as an internal standard.

Interconversion between phenylmagnesium bromide and 3,5-difluoroiodobenzene

A solution of phenylmagnesium bromide prepared from bromobenzene (25 mmol) and magnesium foil (27.5 mg-atom) in THF (28 ml) was filtered under nitrogen to remove excess of magnesium foil. To this Grignard solution was added 3,5-difluoroiodobenzene (25 mmol) at 25°C, and the mixture was subjected to ^{19}F NMR analysis for monitoring the reaction. The intergral ratio of the ^{19}F signal for 3,5-difluorophneylmagnesium bromide to that of 3,5-difluoroiodobenzene was determined as follows: 2.8 after 10 min., 5.5 after 30 min., 8.0 after 2 hr and 8.5 after 5 hr (nearly at equilibrium). ^{19}F NMR (ext. CF_3CO_2H): δ 29.4 ppm, 3,5-difluoroiodobenzene; δ 37.8 ppm, 3,5-difluorophenylmagnesium bromide.

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