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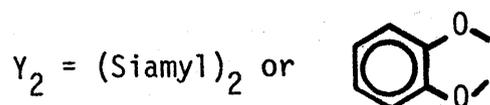
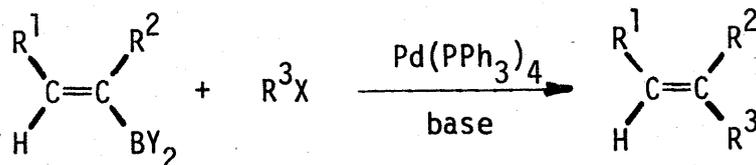
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THE PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF
PHENYLBORONIC ACID WITH HALOARENES
IN THE PRESENCE OF BASES

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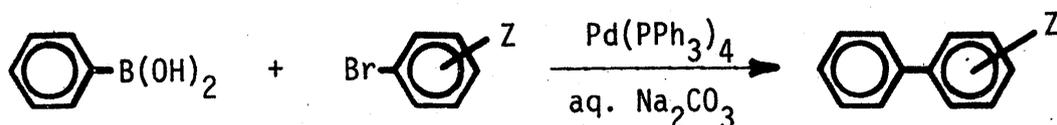
The transition metal-catalyzed reactions of organometallics with organic halides have been extensively studied to prove a new approach to selective formation of carbon-carbon bonds. Recently, such coupling reactions of haloarenes with aryl magnesium¹⁻³ and zinc⁴ compounds in the presence of palladium or nickel complexes have been reported for the synthesis of biaryls. Davidson and Triggs⁵ have previously reported that arylboronic acids react with sodium palladate to give the corresponding biaryls in good yields. The synthetic utility of the dimerization reaction is, however, limited because it requires stoichiometric amounts of the palladium compound. On the other hand, we have recently reported that cross-coupling reactions between alkenylboranes and organic halides such as alkenyl,⁶ alkynyl,⁶ aryl,⁷ allyl,⁸ and benzyl⁸ halides are effectively catalyzed by a catalytic amount of tetrakis(triphenylphosphine)palladium, Pd(PPh₃)₄ in the presence

of suitable bases as indicated in Scheme 1. Although the detailed mechanistic pathway is not clear at present, the reaction should involve a transmetalation step from alkenylboranes to alkenyl-palladiums.



Scheme 1

In this paper, we wish to report that the palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes proceeds smoothly in the presence of bases to give corresponding biaryls in good yields (Scheme 2). At first, we examined the



Scheme 2

effect of reagents, bases, and reaction conditions on the yield of biphenyl in the reaction of phenylboronic acid with halo-benzenes using benzene as a solvent and 3 mole % of $Pd(PPh_3)_4$ as a catalyst. The results are listed in Table I. Although we have not undertaken a detailed study of catalysts, $Pd(PPh_3)_4$ was found

Table I
 Cross-Coupling Reactions between Phenylboronic Acid
 and Halobenzenes under Various Reaction Conditions.^a

PhX, X=	Base	Time (h)	Yield of biphenyl ^b (%)
I	2M-NaOEt/EtOH	6	32
I	2M-NaOH/H ₂ O	6	62
Br	2M-NaOEt/EtOH	3	39
Br	2M-NaOEt/EtOH	6	49
Br	2M-NaOEt/EtOH	10	52
Br	2M-NaOH/H ₂ O	6	76
Br	2M-NaOAc/H ₂ O	6	11
Br	2M-Na ₂ CO ₃ /H ₂ O	6	88
Cl	2M-NaOEt/EtOH	6	0

^aAll reactions were carried out in benzene at the boiling temperature by using 1.0 mmol of halobenzenes, 10% excess of phenylboronic acid, 3 mole % of Pd(PPh₃)₄ and 2 mmol of bases under nitrogen atmosphere. ^bBased on halobenzenes and determined by GLC.

to be effective even in an amount of 3 mole % as the catalyst for the cross-coupling with iodo- and bromobenzenes. Chlorobenzene was quite inert under the same conditions. The effect of bases was also important, because the desired cross-coupling products

were not obtained in any noticeable amounts in the absence of bases. Unlike our palladium-catalyzed reactions⁶⁻⁸ previously reported, relatively weak bases such as sodium carbonate gave high product yields. A comparative reactivity study of bases in the reaction of phenylboronic acid with bromobenzene using 3 mole % of $\text{Pd}(\text{PPh}_3)_4$ in benzene showed the following yields: AcONa in H_2O (11%), EtONa in EtOH (49%), NaOH in H_2O (76%), and Na_2CO_3 in H_2O (88%).

Representative results are summarized in Table II. The aryl-aryl coupling reaction reported here was complete within 6 h at refluxing temperature of benzene when sterically less hindered bromoarenes are used. The reaction with hindered bromoarenes such as mesityl bromide and 1-naphthyl bromide occurred slowly under such conditions. However, the yields can be improved by carrying out the reaction at higher reaction temperatures and for longer reaction times by using toluene as a solvent. Since chloroarenes are inert for the reaction, the formation of p-terphenyl was observed in the reaction with p-dibromobenzene, and p-chlorobiphenyl was selectively produced in the reaction with p-bromochlorobenzene. In the reaction of aryl magnesium halides in the presence of nickel complex,^{1,2} chlorobenzene was reported to react. That reaction, however, does not show such high selectivity observed in the present reaction.

Arylboronic acids are stable in air and quite inert to various functional groups which sometime require protection-deprotection sequence. Consequently, this reaction has a major advantage over cross-coupling reactions using other organometallic compounds

Table II
 Synthesis of Biaryls (Scheme 2).^a

ArX	Solvent	Reaction time, (h)	Yield of biaryl, (%) ^b
o-MePhBr	Benzene	6	94
p-MePhBr	Benzene	6	88
o-MeOPhBr	Benzene	6	99
p-MeOPhBr	Benzene	6	66 (40)
p-ClPhBr	Benzene	6	89 (74) ^c
p-MeO ₂ CPhBr	Benzene	6	(94)
Mesityl bromide	Toluene	17	(80)
1-Naphthyl bromide	Toluene	10	(49)
p-BrPhBr	Toluene	12	(40) ^d

^aThe reactions were carried out by using 10% excess of phenylboronic acid at the refluxing temperature of solvents used. The amount of Pd(PPh₃)₄ was 3 mole%, and the ratio of Na₂CO₃/ArX was 2 for all the cases. ^bBased on the haloarenes employed and determined by GLC. The isolated yields were indicated in parentheses. ^cp-Chlorobiphenyl. ^dp-Terphenyl.

such as Grignard reagents. One of such examples is indicated in the synthesis of p-carbomethoxybiphenyl by the reaction of methyl p-bromobenzoate with phenylboronic acid in Table 2. Furthermore, a wide variety of arylboronic acids are prepared by function-

alization reactions of the parent arylboronic acid such as nitration, oxidation, and halogenation.⁹ Therefore, the present synthesis provides a range of applicability far broader than the procedures previously available.

The following procedure for the preparation of p-chlorobiphenyl is representative. A 50 ml-flask was charged with Pd(PPh₃)₄¹⁰ (0.3 mmol), benzene (20 ml), p-chlorobromobenzene (10 mmol), and an aqueous solution of Na₂CO₃ (10 ml of a 2M solution) under nitrogen atmosphere, and then phenylboronic acid¹¹ (11 mmol) in ethanol (5 ml) was added. The mixture was refluxed for 6 h under vigorous stirring. After the reaction was complete, the residual phenylboronic acid was oxidized by 30%-H₂O₂ (0.5 ml) at room temperature for 1 h. The product was extracted with ether, washed by a saturated NaCl solution, and finally dried over Na₂SO₄. GLC analysis at this stage revealed the formation of p-chlorobiphenyl in a yield of 89%. The residue after evaporation of the solvent was distilled to afford 1.4 g (7.4 mmol, 74%) of p-chlorobiphenyl: b.p. 156°C/15 mmHg (Lit.¹² 293°C) and m.p. 77°C (Lit.¹² 77°C).

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