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SELECTIVE MONO-ALKYLATION AND ARYLATION OF AROMATIC DIHALIDES BY PALLADIUM-CATALYZED CROSS-COUPLING WITH THE GRIGNARD AND ORGANOZINC REAGENTS

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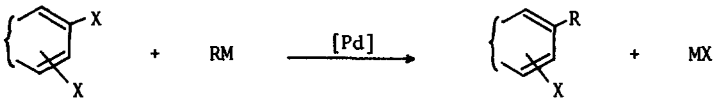
Summary: Dibromobenzene, dibromothiophenes, dichloro- and dibromopyridine are highly selectively mono-alkylated and arylated with Grignard or organozinc reagents in the presence of palladium complexes as catalysts.

The transition metal-catalyzed cross-coupling of organometallic reagents with organic halides have provided a valuable and useful tool for the formation of the carbon-carbon σ-bond.[2] Increasing attention has recently been directed to the functionalized-carbon homologation of organometallics. One of the most remarkable and useful reactions may be the selective mono-alkylation and arylation of α,ω-dibromoalkanes, which has been accomplished by the copper-catalyzed Grignard coupling reaction.[3] There has been virtually no practically useful method for the selective mono-alkylation of aromatic polyhalides. The selective Grignard cross-coupling with $C(sp^2)$-halides catalyzed by nickel[4] or palladium[5] complexes would be promising for the purpose. As we have previously mentioned,[4] however, the nickel-catalyzed Grignard coupling reactions of dichlorobenzenes give rise to the formation of di-alkylated products predominantly even if an equimolar amount of Grignard reagent is used. Although mono-arylation of bromochlorobenzene[5b] and fluoroiodobenzenes[5b,5c] has been achieved by the palladium-catalyzed Grignard coupling, such mixed dihalides are not readily available.

We now find that the palladium-catalyzed coupling reaction is also suitable for the mono-alkylation and arylation of readily available aromatic dihalides containing the same halogen atoms such as dibromobenzenes, dibromothiophenes, dichloro- and dibromopyridine.[6]

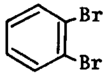
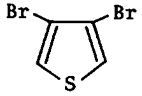
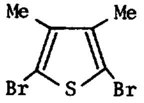
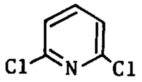
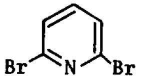


X = Cl, Br; M = MgX or ZnX

Thus, the reaction of one equivalent of an organometallic reagent (the Grignard or organozinc[7] reagent) with a dihalide in the presence of a catalytic amount of a palladium complex gives a substituted monohalide in a satisfactory yield. Representative results are summarized in Table 1. Several characteristic features are as follows. (1) No special technique is necessary and mono-alkylated and arylated products are formed in the range of 52 - 76% yields. In most cases, disubstituted products are formed only in less than several per cent yield. (2) Reactions of 1,2-dibromobenzene with methyl and benzyl Grignard reagents which contain no β-hydrogen were rather slow and about 20% yield of the desired products were obtained under the standard reaction conditions employed in this study. Mono-benzylation, however, could be achieved by using benzylzinc bromide.[7] (3) For the mono-phenylation both of the phenyl Grignard and zinc[7,8] reagents gave essentially the same satisfactory results. (4) The *n*-butyl Grignard reagent, bearing β-hydrogens, gave unsatisfactory results with $Pd(PPh_3)_4$ as a catalyst. The conversion and selectivity, however, could be dramatically improved by using a palladium catalyst containing a bidentate phosphine,[9] 1,4-bis(diphenylphosphino)butane (dppb). The bidentate phosphine-palladium complex is more effective also for the mono-phenylation than unidentate phosphine complexes. (5) Heterocyclic dihalides also undergo the mono-arylation and -benzylation with fairly good selectivity. Comparable reactivity has been observed for 2,6-dichloro- and dibromo-pyridine. While dibromothiophenes reacted smoothly,[10] no reaction was observed with 2,5-dichlorothiophene.

Based on the proposed catalytic cycle[4,5e,11] for the cross-coupling reactions consisting of oxidative addition of an organic halide to a low valent metal species and reductive elimination of a coupling product from a diorganometal complex, the preferential formation of mono-alkylated products from aromatic dihalides with palladium catalysts, not with nickel catalysts, may result from, at least, the following two factors: in comparison with a nickel(0) complex, (1) lower reactivity of palladium(0) species in the oxidative addition to aromatic monohalides, especially to alkylhalobenzenes,[12] and (2) weaker π-interacation of a palladium(0) species with an unsaturated compound.[13] Therefore, the produced mono-alkylated monohaloaromatics may well be

Table 1. Coupling of Aromatic and Heterocyclic Dihalides with Grignard and Organozinc Reagents[a]

Halide	RMgX or RZnX	Catalyst	Conditions[b]			Products,[c] yield (%)[d]		
			Solv.	Temp.	Time (h)	Mono	Di	Rec
	MeMgBr	$Pd(PPh_3)_4$	Et_2O	reflux	20	24	0	78
	n-BuMgBr	$Pd(PPh_3)_4$	Et_2O	reflux	20	15	0	67
	n-BuMgBr	$PdCl_2(dppb)$[e]	Et_2O	reflux	20	76	5	2
	$PhCH_2MgCl$	$Pd(PPh_3)_4$	Et_2O	reflux	20	20	0	79
	$PhCH_2ZnBr$	$Pd(PPh_3)_4$	THF	50°C	16	68	12	9
	PhMgBr	$Pd(PPh_3)_4$	THF	50°C	20	61	2	23
	PhMgBr	$PdCl_2(dppb)$[e]	Et_2O	reflux	20	75	3	11
	PhZnCl	$Pd(PPh_3)_4$	THF	50°C	20	60	4	22
	$PhCH_2ZnBr$	$Pd(PPh_3)_4$	THF	50°C	20	52	6	20
	PhMgBr	$Pd(PPh_3)_4$	THF	50°C	20	72	*f*	*f*
	$PhCH_2ZnBr$	$Pd(PPh_3)_4$	THF	50°C	20	56	13	15
	$PhCH_2ZnBr$	$Pd(PPh_3)_4$	THF	50°C	20	60	15	13

[a] Carried out on a 5 mmol scale. Dihalide/RMg(or Zn)X/catalyst ≈ 1/1/0.01 (molar ratio).
[b] Reaction conditions have not yet been optimized. [c] Mono: mono-alkylated or -arylated product; Di: dialkylated or arylated product; Rec: recovered dihalide. [d] Determined by GLC. [e] dppb = 1,4-bis(diphenylphosphino)butane. [f] Not determined.

replaced from the coordination site by another molecule of dihalide faster than further oxidative addition of the former to a catalytically active palladium species.

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6. The selective mono-methylation (MeMgBr) of 2,6-dichloropyridine in the presence of certain σ-pyridyl-palladium complexes as catalysts has recently been found also by S. Kawaguchi and K. Isobe, Osaka City University (private communication).
7. E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, 42, 1821 (1977).
8. Phenylzinc chloride was prepared by the reaction of the phenyl Grignard reagent with zinc chloride.
9. Certain bidentate phosphine-palladium complexes have recently been shown by two of us to be the most effective catalyst for the cross-coupling of secondary alkyl Grignard reagents with organic halides.[5f]
10. Part of the work on the palladium catalyzed mono-phenylation and benzylation of dibromothiophenes has been presented at the IXth International Conference on Organometallic Chemistry, September 3-7, 1979, Dijon; Abstracts, A19.
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