Palladium-Catalyzed Coupling of Tetraorganotin Compounds with Aryl and Benzyl Halides. Synthetic Utility and Mechanism

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Abstract: Palladium complexes catalyze the coupling of tetraorganotin compounds with benzyl and aryl halides, benzylchlorobis(triphenylphosphine)palladium(II) (**1**) being the catalyst of choice. Various functional groups are tolerated by this reaction and generally high yields of the cross-coupled products are obtained. Oxygen has a considerable accelerating effect on the reaction, whereas triphenylphosphine has little effect. The reaction of substituted bromobenzenes with tetramethyltin catalyzed by **1** is accelerated by electron-withdrawing groups; however, a simple Hammett correlation is not observed. Optically active α-deuteriobenzyl bromide reacts with tetramethyltin to afford optically active α-deuterioethylbenzene with inversion of configuration. Homocoupling is the main reaction observed when lithium or Grignard reagents react with benzyl chloride under the influence of various palladium catalysts.

Introduction

Transition metal complexes are effective catalysts in the coupling of organolithium and Grignard reagents with organic halides, thus providing a method of carbon–carbon bond formation.[1] However, use of these organometallics is limited essentially to unsubstituted halides, benzyl halides reacting anomalously (vide infra). Other coupling methods applying organometallic compounds of less electropositive metals have been developed.[2] The mechanism of the reductive elimination from palladium(II) complexes, which is a crucial step in these catalyzed coupling reactions, has been elucidated[3] and a method for selective and efficient cross-coupling of acid chlorides with tetraorganotin compounds has been developed.[4] This study extends the method for coupling of aryl and benzyl halides with a variety of tetraorganotin compounds. The palladium-catalyzed reaction of benzyl halides with organolithium and Grignard reagents was also studied.

Results and Discussion

Benzyl Chloride and Methyllithium or Methylmagnesium Bromide. Although palladium complexes are good catalysts for the coupling of organic halides with Grignard or organolithium compounds,[1] coupling of benzyl chloride with either methyllithium or methylmagnesium bromide under the influence of various palladium catalysts leads mainly to the homocoupling product, bibenzyl (Table I), whereas the cross-coupling product, ethylbenzene, is formed only in minor amounts.

Interestingly, the reaction of methyllithium with benzyl chloride in a THF-ether solution in the *absence* of catalyst gave a nearly quantitative formation of *trans*-stilbene. A similar reaction was observed between benzyl chloride and *n*-butyllithium in THF;[5] however, extremely low temperatures (−100 °C) were required to obtain good yields of stilbene. The solvent, THF, causes α-hydrogen-metal interconversion to take place, forming α-chlorobibenzyl, which eliminates HCl to give *trans*-stilbene.

Reaction of Benzyl Bromide and Chloride with Tetramethyltin under Argon. In contrast to the reaction of benzyl chloride with methyllithium or methylmagnesium bromide, benzyl bromide reacts with tetramethyltin under the influence of palladium catalysts to yield mainly the cross-coupled product, ethylbenzene, with almost no bibenzyl being formed (eq 1).

$$\mathrm{PhCH_2Br + Me_4Sn \xrightarrow{\text{"Pd"}} PhCH_2CH_3 + Me_3SnBr} \quad (1)$$

The reaction requires a highly polar solvent, for example, hexamethylphosphoramide (HMPA) or *N*-methylpyrilidonone (NMP), no reaction taking place in THF (Table II). The most effective catalysts are benzylchlorobis(triphenylphosphine)palladium(II) (**1**), benzylbromobis(triphenylphosphine)palladium(II) (**2**), and tetrakis(triphenylphosphine)palladium(0) (**3**), the first two being preferred since the last one is air sensitive and less convenient to handle. Benzylchloro-1,2-bis(diphenylphosphinoethane)palladium(II) (**4**) is much less effective, as seen also in the reactions of benzyl halides with methylmagnesium bromide or methyllithium. The reaction rates using the complexes **1**, **3**, or **1** along with 2 mol equiv of triphenylphosphine are essentially the same (Table III), added triphenylphosphine having little effect on the reaction.

The reaction of benzyl chloride with tetramethyltin in HMPA catalyzed by **1** is very slow, yielding only 2% ethylbenzene after 20 h at 62 °C under argon, leaving 97% of the benzyl chloride unreacted. Bromobenzene is even less reactive under these conditions, all these facts being in accordance with the oxidative addition being the rate-determining step.

The reaction (eq 1) is zero order both with respect to benzyl bromide and tetramethyltin (Figure 1). This is consistent with a rate-determining oxidative addition of benzyl bromide to palladium.

Reactions of Organotin Compounds with Organic Halides in Air. Under an inert atmosphere, the reaction between organotin compounds and organic halides catalyzed by palladium is practically limited to compounds that undergo very easy oxidative addition, e.g., benzyl bromide or acid halides.[4] In the presence of oxygen, the reaction can be carried out with other organic halides, provided that they do not contain β-hydrogens. Thus, benzyl chloride and aromatic bromides react normally. Various functional groups, including the ketone function, are tolerated by this reaction, a feature that makes this coupling method advantageous over methods applying Grignard or organolithium compounds. A large variety of organotin compounds can be employed, thus effecting methylation, butylation, phenylation, vinylation, and benzylation of benzyl and aromatic halides. When unsymmetrical organotin compounds are employed, phenyl and vinyl are transferred in preference to methyl and butyl, respectively (Table I, entries 4 and 5). This is consistent with the observation that trimethylvinyltin transfers only the vinyl group upon reaction with platinum(II) complexes.[6] Arylation of platinum(II) complexes has been carried out with trimethylaryltin.[7] Further, a tin-bound benzyl group transfers in preference to methyl (entry 6). Use of un-

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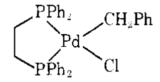
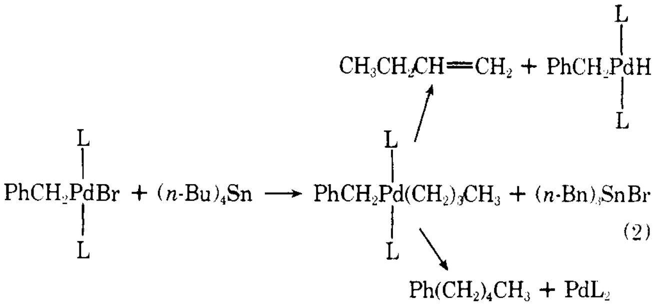
Table I. Reaction of Benzyl Chloride with Methyllithium and Methylmagnesium Bromide. Influence of Various Catalysts[a]

			yield,[b] %					
entry	catalyst	reagent	$PhCH_2$-CH_2Ph	*trans*-PhCH=CHPh	$PhCH_2CH_3$	$PhCH_3$	$PhCH_2Cl$	material balance, %
1	$PhCH_2Pd(PPh_3)_2Cl$ (**1**)	MeLi	58.1	23.2	9.0	0.5	0.0	90.8
2	none	MeLi	4.8	75.0	2.5	0.0	0.0	82.3
3	$PhCH_2Pd(PPh_3)_2Cl$[c]	MeLi	10.9	0.0	3.4	0.8	76.1	91.2
4		MeLi	7.2	37.9	2.4	0.4	35.2	83.1
5	$(PPh_3)_2PdCl_2$	MeLi	51.0	19.2	11.8	0.0	0.0	82.0
6	$PhCH_2Pd(PPh_3)_2Cl$	MeMgBr	67.4	0.0	12.2	18.6	0.0	98.2
7	none	MeMgBr	0.0	0.0	0.0	0.0	100.0	100.0
8	$(PPh_3)_2PdCl_2$	MeMgBr	62.5	0.0	10.1	0.0	24.6	97.2

[a] Reactions utilizing methyllithium were performed in THF-ether (2:1) under argon at 25 °C, $[PhCH_2Cl] = 0.45$ M, [MeLi] = 0.54 M, [cat] = 0.87×10^{-2} M. Reactions with methylmagnesium bromide were carried out in THF-ether (1:1) under argon at 65 °C, $[PhCH_2Cl] = 0.34$ M, [MeMgBr] = 1.44 M, [cat] = 0.65×10^{-2} M. [b] Based on benzyl chloride. [c] In ether.

symmetrical tetraorganotins with only one group of the kind to be transferred generally is more efficient.

The yields of the coupled products are generally high and are paralleled by the yield of the triorganotin halide, consistent with the consumption of the tetraorganotin compound only in the cross-coupling reaction. There is, however, one exception; the reaction of benzyl bromide with tetra(*n*-butyl)tin yields only 42.1% of amylbenzene, whereas 89.3% of tri(*n*-butyl)tin bromide is formed (Table IV, entry 3). This can be explained by coupling of the benzylpalladium complex with the organotin compound to form a dialkylpalladium(II) species that undergoes both β elimination and reductive elimination (eq 2).



$$PhCH_2\overset{L}{\underset{L}{Pd}}Br + (n\text{-}Bu)_4Sn \longrightarrow PhCH_2\overset{L}{\underset{L}{Pd}}(CH_2)_3CH_3 + (n\text{-}Bn)_3SnBr \quad (2)$$

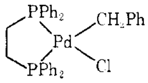
$$\nearrow CH_3CH_2CH{=}CH_2 + PhCH_2\overset{L}{\underset{L}{Pd}}H \qquad \searrow Ph(CH_2)_4CH_3 + PdL_2$$

Although 1-butene is also formed in the reaction, the reductive elimination process is fast enough to compete with β elimination. Thus, tetraorganotin compounds having groups containing β hydrogens can be utilized, although lower yields are obtained. Alkyl halides containing β hydrogens cannot be used, since in addition to the β-elimination problem, the oxidative addition process in most of the cases is too slow.

The reaction also can be catalyzed by tetrakis(triphenylphosphine)palladium(0) (**3**), in spite of the fact that this compound is air sensitive, provided that the complex is added to a solution of the organic halide and not in the reverse order. The large excess of the organic halides converts the palladium(0) complex into an air-stable palladium(II) complex by oxidative addition before it has a chance to react with oxygen. Thus, yields of 83.9% ethylbenzene and 92.1% trimethyltin bromide are obtained when benzyl bromide reacts with tetramethyltin for 5 h at 65 °C in HMPA in air using **3** as a catalyst.

It is necessary that highly polar solvents, e.g., HMPA, be used even when oxygen is present. Thus, reaction of benzyl bromide with tetramethyltin in THF under air catalyzed by **1** yielded only 1% of ethylbenzene after 17 h at 65 °C. The end of the reaction, when carried out under air, is clearly visualized, since, as soon as all the organic halide is consumed, colloidal Pd-metal precipitates and the clear yellow solution turns black.

Table II. Reactions of Benzyl Bromide with Tetramethyltin under Argon[a]

catalyst	solvent	% yield $PhCH_2CH_3$[b]	% recovered $PhCH_2Br$
$PhCH_2Pd$-$(PPh_3)_2Cl$ (**1**)	HMPA	70.0	3.2
none	HMPA	0.0	100.0
1	THF	0.0	94.6
1	THF + 2,6-lutidine[c]	0.0	95.7
1	NMP	55.5	25.8
1	tetramethylurea	1.9	93.7
1	ethanol	0.0	0.0[d]
 (**4**)	HMPA	14.5	75.6
$Pd(PPh_3)_4$ (**3**)	HMPA	69.8	4.1
$(PPh_3)_2PdCl_2$	HMPA	31.0	58.8
$PhCH_2Pd$-$(PPh_3)_2Br$ (**2**)	HMPA	67.3	2.9

[a] All reactions were run at 62 °C for 20 h. [b] Based on benzyl bromide. [c] One equivalent of 2,6-lutidine per equivalent of catalyst. [d] 74.6% of benzyl methyl ether was formed.

Table III. Reaction of Benzyl Bromide with Tetramethyltin (8 h, 64 °C) under Argon

	yield,[a] %	
catalyst	$PhCH_2CH_3$	Me_3SnBr
$PhCH_2Pd(PPh_3)_2Cl$ (**1**)	26.9	24.6
1 + $2PPh_3$	25.3	25.3
$Pd(PPh_3)_4$ (**3**)	28.5	29.4

[a] Based on benzyl bromide.

The considerable oxygen effect on the rate of the reaction of tetraorganotins and organic bromides catalyzed by **1** (Table V; compare also Table IV with Table II) can be put to use by conducting the reactions under an atmosphere of pure oxygen if faster rates are needed. The manipulation and workup of the reaction are very simple. HMPA is removed by water extraction, and the residue is purified by distillation or crystallization. Another method that can be utilized to separate the product from the triorganotin halide formed in the reaction is the addition of an alcoholic solution of KF to the ethereal solution of the product. The highly insoluble triorganotin fluoride is separated by filtration.

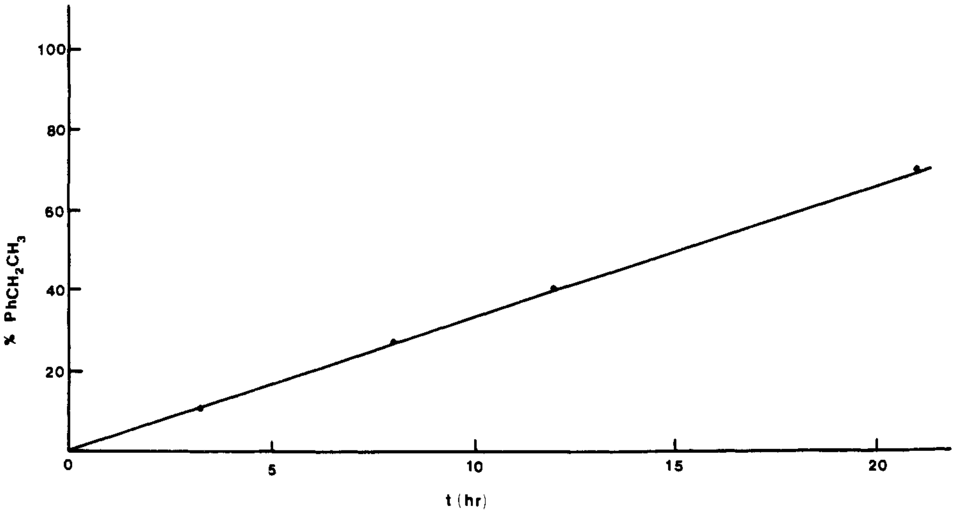
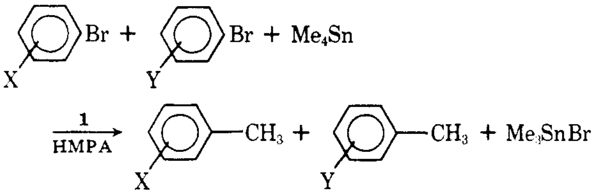


Figure 1. Reaction of benzyl bromide with tetramethyltin in HMPA under argon at 63 °C, catalyzed by **1**.

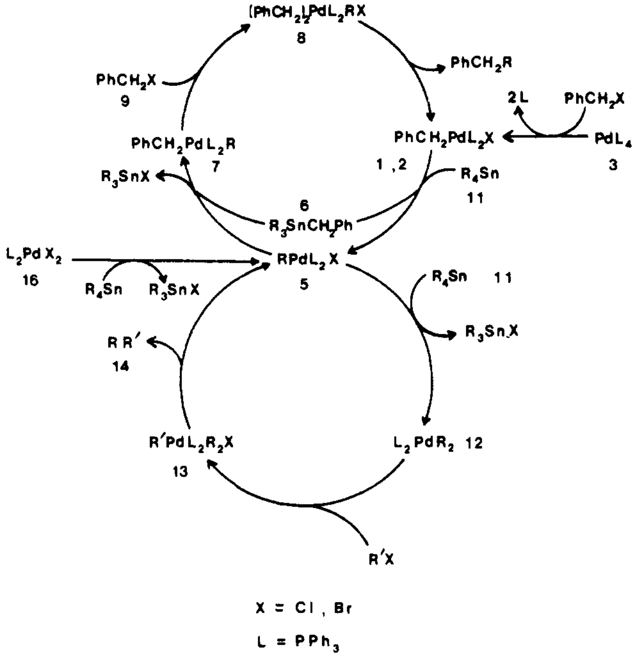
Mechanism. A series of competitive reactions between mixtures of various substituted bromobenzenes and a limited amount of tetramethyltin in HMPA using **1** as a catalyst was carried out in order to determine the substituent effect on the reaction (eq 3). The relative rates were calculated based on the relative amounts of substituted toluenes formed (Table VI).



(3)

The reaction clearly is accelerated by electron-withdrawing substituents on the aryl bromide, analogously to that observed for the oxidative addition of aromatic halides to tetrakis(triphenylphosphine)palladium(0).[8] The relative rates obtained for various meta and para substituents have been plotted against the Hammett σ values (Figure 2).[9] Two linear correlations, rather than one, can be drawn, one for electron-withdrawing substituents and the other for electron-donating groups. The ρ value for the former ($\rho = 3.38$) is larger than for the latter ($\rho = 1.29$), indicating higher sensitivity to substituent effects for electron-withdrawing groups. Similar effects have been observed in the oxidative addition reaction of aryl halides to tris(triphenylphosphine)nickel(0).[10] In view of the similarity between the substituent effect on oxidative addition and on the reaction between organic halides and tetraorganotin compounds catalyzed by **1**, the oxidative addition of the halide to palladium most likely is rate determining. This is also supported by the observed reactivity order $PhCH_2Br > PhCH_2Cl > PhBr$, and by the observation that the fast β-elimination process is of comparable rate with the reductive elimination reaction (vide supra). If the oxidative addition step is indeed rate determining, oxygen can accelerate the reaction by acting as an electron acceptor and initiating a radical oxidative addition process that is faster than the nucleophilic displacement[11] that takes place under inert atmosphere. Both radical[12] and nucleophilic displacement mechanisms[13] have been observed for palladium complexes. The reaction between benzyl bromide and tetramethyltin catalyzed by **1** in the presence of the radical scavenger 3,3′,5,5′-tetra-*tert*-butyl-4,4′-dihydroxydiphenylmethane gave only 29.3% of ethylbenzene after 17 h at 63 °C, whereas a similar experiment in the absence of the scavenger yielded ethylbenzene quantitatively. The rate of oxidative addition of alkyl halides to palladium(0) and platinum(0) has been shown to be retarded by radical scavengers in a number of cases.[10,14] Oxygen has been demonstrated to increase the rate of reductive elimination from nickel(II) complexes, and was proposed to act as an electron acceptor;[15] however, oxygen as well as other electron acceptors have no effect on the reductive elimination reaction of palladium(II) complexes.[3]

Scheme I



A mechanism for the reaction of tetraorganotin compounds with organic halides catalyzed by various palladium complexes is outlined in Scheme I, and is based partly on the results obtained in a study of the reductive elimination reaction of palladium.[3] Benzyl halides probably react both according to the upper cycle and the lower cycle, whereas other organic halides react only according to the lower one. The catalyst, benzylhalogenobis(triphenylphosphine)palladium(II) (**1**, **2**), undergoes transmetalation with the tetraorganotin compound to replace the benzyl group (not halogen) to form the complex organohalogenobis(triphenylphosphine)palladium(II) (**5**) and benzyltriorganotin (**6**). This has been shown to take place with a variety of benzylpalladium complexes and tetramethyltin[3] (eq 4). Complex **5** reacts with **6** to give the diorganopalladium

Table IV. Reaction of Organic Halides with Organotin Compounds

$$Rx + R'_4Sn \xrightarrow[HMPA]{1} RR' + R'_3SnX$$

entry	RX	R'_4Sn	RR', (% yield)	R_3SnX (% yield)[a]
1	$PhCH_2Br$	Me_4Sn	$PhCH_2CH_3$ (82.0)	Me_3SnBr (85.3)
2	$PhCH_2Br$	Ph_4Sn	$PhCH_2Ph$ (91.3)	*b*
3	$PhCH_2Br$	$(n\text{-}Bu)_4Sn$	$Ph(CH_2)_4CH_3$ (42.1)[c]	$(n\text{-}Bu)_3SnBr$ (89.3)
4	$PhCH_2Br$	$(n\text{-}Bu)_3SnCH{=}CH_2$	$PhCH_2CH{=}CH_2$ (100.0)	$(n\text{-}Bu)_3SnBr$ (95.1)
5	$PhCH_2Br$	Ph_3SnMe	$PhCH_2Ph$ (95.3)	*b*
6	$PhCH_2Br$	Me_3SnCH_2Ph	$PhCH_2CH_2Ph$ (89.5)	Me_3SnBr (95.2)
7	$PhCH_2Br$	Me_4Sn	$PhCH_2CH_3$ (61.9)	Me_3SnCl (68.8)
8	PhBr	Me_4Sn	$PhCH_3$ (88.6)	Me_3SnBr (92.1)
9	PhBr	Ph_4Sn	PhPh (78.2)	*b*
10	$4\text{-}CH_3C_6H_4Br$	Me_4Sn	$4\text{-}CH_3C_6H_4CH_3$ (84.3)	Me_3SnBr (85.7)
11	$4\text{-}CH_3OC_6H_4Br$	Me_4Sn	$4\text{-}CH_3OC_6H_4CH_3$ (85.1)	Me_3SnBr (94.3)
12	$4\text{-}FC_6H_4Br$	Me_4Sn	$4\text{-}FC_6H_4CH_3$ (89.1)	Me_3SnBr (87.2)
13	$4\text{-}CH_3COC_6H_4Br$	Me_4Sn	$4\text{-}CH_3COC_6H_4CH_3$ (95.4)	Me_3SnBr (98.7)

[a] Based on RX. [b] Not determined. [c] 1-Butene is also formed.

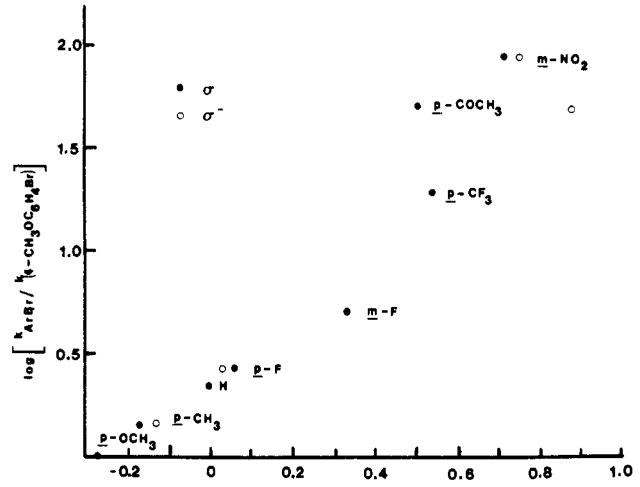
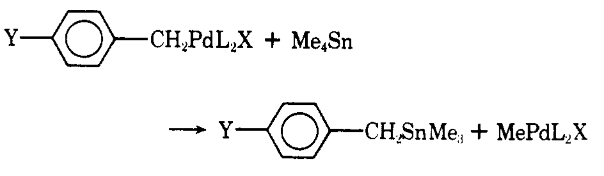


Figure 2. Hammett plot of the reaction of substituted bromobenzenes with tetramethyltin catalyzed by **1**.



(4)

complex **7** that undergoes further oxidative addition of another benzyl halide to form the palladium(IV) complex **8**. This complex undergoes reductive elimination to yield the coupling product **9** and the starting complex **1** (**2**), thus completing the upper cycle.

When tetrakis(triphenylphosphine)palladium(0) (**3**) is used as a catalyst, it oxidatively adds benzyl halide to form complex **1** or **2** and enters the cycle. Actually, a reaction of **3** with 2 mol of benzyl bromide and tetramethyltin, under the same reaction conditions as those in which the catalytic reaction is carried out, yields the complex bromomethylbis(triphenylphosphine)palladium(II) (**10**) (eq 5). Complex **10** was also isolated from the reaction of benzylbromobis(triphenylphosphine)palladium(II) (**2**) and *p*-methylbenzyl bromide with tetramethyltin under the same conditions; *p*-methylethylbenzene and ethylbenzene were also formed.

$$PdL_4 + 2PhCH_2Br + Me_4Sn \xrightarrow[2L]{} \underset{\mathbf{10}}{MePdL_2Br} + PhCH_2SnMe_3 + PhCH_2P^+Ph_3Br^- \quad (5)$$

$L = PPh_3$

Table V. Effect of Oxygen on the Reaction of Benzyl Bromide with Tetramethyltin[a]

oxygen, mmol	yield (%)[b] of ethylbenzene
6.0	11.3
135.7	38.8
690.0	81.2

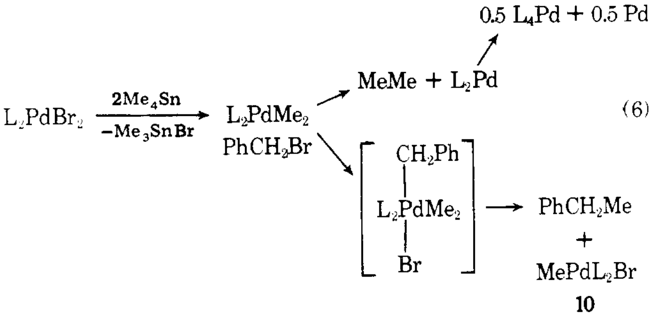
[a] A solution of 3.38 mmol of benzyl bromide, 7.22 mmol of tetramethyltin, and 5×10^{-2} mmol of **1** in 2 mL of HMPA was heated at 62 °C for 2 h in a 30-mL sealed tube under an atmosphere of argon containing the specified oxygen amount. [b] Based on benzyl bromide.

Table VI. Relative Rates of the Reactions of Substituted Bromobenzenes with Tetramethyltin Catalyzed by **1**[a]

substituent	rel rate $k(ArBr)/k(4\text{-}CH_3OC_6H_4Br)$
p-OCH_3	1.00
p-CH_3	1.46
H	2.18
p-F	2.65
m-F	5.06
p-CF_3	19.50
p-$COCH_3$	53.14
m-NO_2	87.93

[a] In HMPA, under argon, at 63 °C.

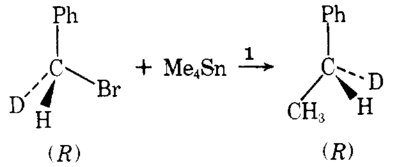
Another pathway requires the reaction of **5** with tetraorganotin **11** rather than with **6**. This pathway can take place, although **6** is evidently much more reactive than **11**, since the latter is present in large excess, especially at the early stages of the reaction. This is the only pathway that operates for organic halides *other* than benzyl halides, since after the first cycle all of **6** is consumed. Halogen-for-alkyl (aryl) metathesis between **5** and **11** yields dialkylpalladium complex **12**, which then undergoes oxidative addition of an organic halide to give palladium(IV) complex **13**. Reductive elimination of **13** yields the coupling product **14** and regenerates complex **5**. Dimethylbis(triphenylphosphine)palladium(II) (**15**) has been demonstrated to react with benzyl bromide at 25 °C to afford nearly quantitative yields of ethylbenzene and bromomethylbis(triphenylphosphine)palladium(II) (**10**).[3] Only minor amounts of ethane are detected, a product that is formed when **15** decomposes at 40 °C in the absence of benzyl bromide. Thus, a palladium(IV) intermediate such as **13** was implicated in the reductive elimination step. When dihalogenobis(triphenylphosphine)palladium(II) (**16**) is the catalyst, it reacts with tetraorganotin compound **11** to give the complex **5**. Thus, dibromobis(triphenylphosphine)palladium(II) reacts with tetramethyltin to form ethane and metallic palladium, whereas in the presence of benzyl bromide, bromomethylbis(triphenylphosphine)palladium(II) (**10**) and ethylbenzene are formed, while even traces of ethane could not be detected (eq 6).



(6)

The central role of complex **5** is supported by the fact that **10** is an efficient catalyst for the reaction, yielding 90.5% ethylbenzene in the reaction of benzyl bromide and tetramethyltin under the conditions in Table IV.

In order to determine the stereochemistry of the process, (*R*)-(−)-α-deuteriobenzyl bromide, $[\alpha]^{25}_{\mathrm{D}}$ −0.737 ± 0.002° (61.4 ± 4% ee),[16] was allowed to react with tetramethyltin in HMPA *under argon* at 63 °C using **1** as a catalyst. (*R*)-(−)-α-Deuterioethylbenzene was formed, $[\alpha]^{25}_{\mathrm{D}}$ −0.059 ± 0.003°, 8 ± 1% ee.[17] The overall process results, therefore, in 13 ± 2% inversion of configuration (eq 7). However, the stereospecificity of the process is probably much higher, since a control experiment carried out in the absence of tetramethyltin showed that (*R*)-(−)-α-deuteriobenzyl bromide undergoes complete racemization under the reaction conditions. According to Scheme I, α-deuterioethylbenzene can be produced either by oxidative addition to **7** followed by reductive elimination of palladium(IV) complex **8** formed, or by oxidative addition to complex **12** followed by reductive elimination of palladium(IV) complex **13**. Whatever the pathway, a two-step process, oxidative addition to form a palladium(IV) complex and reductive elimination of this complex, is involved. Oxidative addition of (*R*)-(−)-α-deuteriobenzyl bromide to tetrakis(triphenylphosphine)palladium (**3**) takes place with 69 ± 10% net inversion of configuration at carbon.[3] Inversion of configuration of other benzylic halides upon oxidative addition to **3** and to tris(triethylphosphine)palladium(0) has also been observed, and an S_N2-like mechanism in which the palladium(0) complex serves as a nucleophile has been proposed.[11] Assuming that electron-rich dialkylpalladium(II) complex **7** or **12** undergoes oxidative addition in the absence of oxygen by the same mechanism, then the reductive elimination step takes place with *retention* of configuration at the benzylic carbon. This result is consistent with the stereochemistry of the reaction of dimethylbis(triphenylphosphine)palladium(II) with optically active α-deuteriobenzyl bromide.[3]



(7)

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were obtained using a JEOL MH-100 or a Varian EM-360 spectrometer with Me_4Si as an internal standard in $CDCl_3$. GLC analyses were performed on a Varian Aerograph 700 using a 0.25 in. × 6 ft column packed with 20% Carbowax 20M on Chromosorb W (column A) or a 0.25 in. × 6 ft column packed with 15% DEGS on Chromosorb W (column B). IR spectra were measured with a Beckman Acculab 3 instrument.

Alkyl and aryl halides and tetramethyltin, tetrabutyltin, tetraphenyltin, and triphenylmethyltin were obtained commercially and used as received. Methyllithium and methylmagnesium bromide were titrated before use. HMPA, NMP, and tetramethylurea were dried over 4 Å molecular sieves; THF was dried on sodium and distilled before use. Tributylvinyltin,[18] tetrakis(triphenylphosphine)palladium(0),[19] benzylchlorobis(triphenylphosphine)palladium(II),[20] and benzylbromobis(triphenylphosphine)palladium(II) were prepared according to published procedures.

Reactions of Benzyl Chloride with Methyllithium (Table I). To a stirred solution of 6.5 × 10^{-2} mmol of the palladium catalyst (Table I) and 0.39 mL (3.4 mmol) of benzyl chloride in 5 mL of THF under argon was added dropwise 2.50 mL (4.03 mmol) of a solution of 1.61 M methyllithium in ether. The solution was heated to a gentle reflux and was stirred for 70 min, after which it was cooled in an ice bath and hydrolyzed with 10 mL of water. The organic phase was separated and the water phase was washed with ether. Hexane (20 mL) was added to the combined organic solutions, and the mixture was filtered. The filtrate was analyzed by GLC (column B, 125–235 °C) and the products were identified by comparison of retention times with those of authentic samples. Isolation of the products by preparative GLC afforded samples for which the melting point, ^{1}H NMR, and IR spectra were obtained for further identification.

Reactions of Benzyl Chloride with Methylmagnesium Bromide (Table I). To a stirred solution of 6.5 × 10^{-2} mmol of the palladium catalyst (Table I) and 0.39 mL (3.4 mmol) of benzyl chloride in 5 mL of THF under argon was added 5.0 mL (14 mmol) of a solution of 2.88 M methylmagnesium bromide in ether. After the solution was heated to reflux under argon pressure (10 mmHg) at 65 °C for 3.5 h, it was hydrolyzed with cold dilute HCl. The water layer was separated and washed with ether. The combined washings and organic layer were dried over $CaCl_2$ and analyzed by GLC as described for the reaction of benzyl chloride with methyllithium.

Reactions of Benzyl Bromide and Chloride with Tetramethyltin (Table II). A solution of 5 × 10^{-2} mmol of the palladium catalyst (Table II), 600 mg (3.51 mmol) of benzyl bromide, and 1.00 mL (7.22 mmol) of tetramethyltin in 2 mL of solvent was stirred at 62 °C for 20 h. After the mixture cooled to room temperature, 5 mL of ether was added followed by 5 mL of water. The ether layer was separated and the water layer was washed with ether and pentane. Addition of the washings to the ether solution caused precipitation, and the mixture was filtered. The filtrate was analyzed by GLC (column A, 135–180 °C) and the products were identified by comparison of retention times. Isolation of the products by preparative GLC afforded samples for which the ^{1}H NMR and IR spectra were obtained for further identification.

General Procedure for Coupling of Tetraorganotin Compounds with Organic Halides (Table IV). To a solution of 7.1 mmol of the organic halides in 4 mL of hexamethylphosphoramide (HMPA) was added 40 mg (0.05 mmol) of **1** and 8.0 mmol of the tetraorganotin compound (except when tetraphenyltin was used, in which case a suspension of the tin compound in 28.7 mL of HMPA was added). The yellow solution was heated at 65 °C with stirring under air in a sealed tube until blackening occurred (1–20 h). The solution was cooled to room temperature and 5 mL of water was added. The mixture was extracted with ether, and the ether solution was washed with water, dried over $MgSO_4$, and analyzed by GLC. Removal of the solvent by evaporation yielded the crude product that was purified by distillation or crystallization. In cases where very volatile materials were formed (e.g., 1-butene), vacuum transfer to a liquid nitrogen cold trap was performed before addition of water, and the volatile materials were analyzed by GLC, ^{1}H NMR, and IR.

Determination of Relative Rates of Coupling of Aryl Bromides with Tetramethyltin. To a solution of 52 mg (0.069 mmol) of benzylchlorobis(triphenylphosphine)palladium(II) (**1**) and the two aromatic bromides (4.3 mmol each) in 4 mL of HMPA under argon was added 0.5 mL (3.6 mmol) of tetramethyltin, and the solution was heated with stirring at 65 °C for 42 h. After the mixture had cooled to room temperature, 10 mL of water was added and the mixture was extracted with 4 × 20 mL of ether. The amounts of both the substituted toluenes formed and the unreacted aryl bromides were determined by GLC analysis.

Ethylbenzene. This compound was prepared from benzyl bromide and tetramethyltin according to the general procedure using either benzylchlorobis(triphenylphosphine)palladium(II) or tetrakis(triphenylphosphine)palladium(0) as catalysts. Blackening took place after 5 h, and the product was isolated in 82.0% yield by addition of water to the reaction mixture and extraction with pentane, followed by fractional distillation: bp 135–136 °C (760 mm); ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 5 H, phenyl), 2.68 (q, J = 7 Hz, 2 H, CH_2), 1.25 (t, J = 7 Hz, 3 H, CH_3).

Diphenylmethane. Benzyl bromide was allowed to react with tetraphenyltin according to the general procedure, and blackening took place after 4 h. Water (10 mL) was added followed by 20 mL of ether, and the precipitated triphenyltin bromide was removed by filtration. The organic phase was separated and the water phase was extracted with 3 × 20 mL of ether. The combined organic solutions were washed with 2 × 20 mL of water and dried over $MgSO_4$. The solvent was removed by evaporation to give white crystals of the products that were washed with a small amount of cold pentane and dried in vacuo: mp 26–27 °C (lit.[21] 25.3 °C); ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 10 H, aromatic), 3.88 (s, 2 H, CH_2). The yield was 91.3%.

Methyl-*p*-tolyl Ketone. This compound was prepared from *p*-bromoacetophenone and tetramethyltin according to the general procedure and was purified by vacuum distillation to give colorless needles: bp 75–76 °C (2 mmHg); mp 28 °C (lit.[21] 28 °C); ^{1}H NMR (CCl_4) δ 7.9–7.1 (m, 4 H, phenyl), 2.4 (s, 3 H, $COCH_3$), 2.3 (s, 3 H, CH_3).

Biphenyl. This compound was prepared from bromobenzene and tetraphenyltin according to the general procedure in 78.2% yield after crystallization from hexane: mp 70–71 °C (lit.[21] 71 °C); ^{1}H NMR ($CDCl_3$) δ 7.20–7.75 (m, aromatic).

Allylbenzene. This compound was prepared from benzyl bromide and tributylvinyltin according to the general procedure and isolated in 95.1% yield after distillation: bp 43–45 °C (4 mmHg) (lit.[21] 156 °C (760 mmHg)); ^{1}H NMR (CCl_4) δ 7.14 (s, 5 H, phenyl), 5.85 (m, 1 H, CH=), 5.02 (m, 1 H, cis terminal proton), 4.99 (m, 1 H, trans terminal proton), 3.33 (d, J = 7 Hz, 2 H, CH_2).

Bibenzyl. This compound was prepared in 89.5% yield from benzyl bromide and trimethylbenzyltin according to the general procedure: mp 51–52 °C (lit.[21] 52.2 °C); ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 10 H, aromatic), 2.88 (s, 4 H, CH_2).

Reaction of Benzylbromobis(triphenylphosphine)palladium(II) with *p*-Methylbenzyl Bromide and Tetramethyltin. Formation of *trans*-Bromomethylbis(triphenylphosphine)palladium(0), *p*-Methylethylbenzene, Ethylbenzene, *p*-Xylene, and Toluene. A suspension of 327 mg (0.408 mmol) of benzylbromobis(triphenylphosphine)palladium(II), 155 mg (0.837 mmol) of *p*-methylbenzyl bromide, and 1.000 mL (7.224 mmol) of tetramethyltin in 2 mL of hexamethylphosphoramide was stirred under argon at 62 °C for 22 h. The initial orange color changed to pale yellow and a white solid separated. After cooling the mixture to room temperature, 5 mL of ether was added and the white *trans*-bromomethylbis(triphenylphosphine)palladium(II) was isolated by filtration, washed with ether and pentane, and dried in vacuo to give 239 mg (66.2%) of product; the melting point, ^{1}H NMR, and IR were identical with those described before for *trans*-bromomethylbis(triphenylphosphine)palladium(II).[3] GLC analysis of the mother liquor (column A, 130 °C) showed the presence of *p*-methylethylbenzene (36.5%), ethylbenzene (31.0%), toluene (9.6%), and *p*-xylene (2.1%).

Reaction of Tetrakis(triphenylphosphine)palladium(0) with Benzyl Bromides and Tetramethyltin. (a) Two Equivalents of Benzyl Bromide. A suspension of 477 mg (0.410 mmol) of tetrakis(triphenylphosphine)palladium(0), 144 mg (0.840 mmol) of benzyl bromide, and 0.50 mL (3.6 mmol) of tetramethyltin in 5 mL of hexamethylphosphoramide was stirred at 66 °C; after 5 min the complex dissolved completely forming a dark orange solution. A white precipitate appeared after 1 h and the solution turned gradually to pale yellow. Heating was continued for 3 h, after which the mixture was cooled to room temperature and the white *trans*-bromomethylbis(triphenylphosphine)palladium(II) was collected by filtration, washed with ether and pentane, and dried in vacuo to give 205 mg; mp 188–189 °C; ^{1}H NMR, ^{31}P NMR, and IR spectra were identical with those we described before.[3] Addition of ether–pentane (1:1) to the mother liquor caused further precipitation (115 mg) of this complex, which was collected by filtration and washed with ether and pentane. The overall yield of the complex was 96.7%. GLC analysis of the mother liquor showed the presence of ethylbenzene (8.2% based on benzyl bromide).

Similar results were obtained when *p*-methylbenzyl bromide was used instead of benzyl bromide; a 92.3% yield of bromomethylbis(triphenylphosphine)palladium(II) and a 7.5% yield of *p*-methylethylbenzene were obtained.

(b) One Equivalent of *p*-Methylbenzyl Bromide. In a similar reaction, a suspension of 403 mg (0.349 mmol) of tetrakis(triphenylphosphine)palladium(0), 64.1 mg (0.346 mmol) of *p*-methylbenzyl bromide, and 0.42 mL (3.0 mmol) of tetramethyltin in 4.2 mL of hexamethylphosphoramide was stirred under argon at 65 °C. Complete dissolution resulted after 10 min and stirring was continued for 4 h, during which time a yellow precipitate appeared. After cooling the mixture at 0 °C for 4 h, it was filtered under argon and the lemon yellow precipitate was washed well with ether and hexane and dried in vacuo to give 196 mg of tetrakis(triphenylphosphine)palladium(0); mp 114–116 °C; IR and ^{1}H NMR spectra were identical with those of an authentic sample. Upon addition of a solution of ether–hexane (1:1) to the mother liquor, a yellow precipitate formed which was isolated by filtration under argon and was washed with hexane and dried in vacuo to give 88.5 mg of what was shown by ^{1}H NMR and TLC to be a mixture of bromomethylbis(triphenylphosphine)palladium(II) (63.0 mg, 22.5% yield) and tetrakis(triphenylphosphine)palladium(0) (25.5 mg, overall yield 55.0%), mp of mixture 182–188 °C.

Reaction of Dibromobis(triphenylphosphine)palladium(II) and Tetramethyltin. (a) A suspension of 304 mg (0.385 mmol) of dibromobis(triphenylphosphine)palladium(II) and 400 μL (2.89 mmol) of tetramethyltin was heated with stirring at 64 °C under argon for 3 h during which it turned black. The volatile materials were transferred in vacuo to a liquid nitrogen cold trap containing 0.5 mL of $CDCl_3$. The ^{1}H NMR spectrum of the transferred material showed the presence of ethane: δ 0.795 (s).

(b) Addition of *p*-Methylbenzyl Bromide. A yellow suspension of 325.5 mg (0.412 mmol) of dibromobis(triphenylphosphine)palladium(II), 76.3 mg (0.412 mmol) of *p*-methylbenzyl bromide, and 500 μL (3.61 mmol) of tetramethyltin in 4.7 mL of HMPA was stirred at 64 °C under argon, and the precipitate turned white after ca. 10 min. After 3.5 h the mixture was cooled to room temperature, and the white precipitate was isolated by filtration, and was washed with ether and hexane to give 201 mg (67.3% yield) of bromomethylbis(triphenylphosphine)palladium(II); melting point, ^{1}H NMR, and IR spectra were identical with those described.[3] Upon addition of hexane to the filtrate, a yellow precipitate was isolated by filtration and was washed with hexane to give 54 mg of a mixture that consisted (by ^{1}H NMR) of bromomethylbis(triphenylphosphine)palladium(II) (46 mg) and small amounts of unidentified complexes.

Similar results were obtained when a molar ratio of 2:1 *p*-bromobenzyl bromide–dibromobis(triphenylphosphine)palladium(II) was used.

(*R*)-(−)-α-Deuteriobenzyl Bromide. (*S*)-(+)-α-Deuteriobenzyl alcohol, $[\alpha]^{25}_{D}$ +1.211° (neat, l = 1), 76.6 ± 0.5% ee, was prepared in 80.3% yield by reduction of α-deuteriobenzaldehyde, 100 ± 0.1% deuterium per molecule, with 9-BBN.[22] Reaction of the alcohol with PBr_3 yielded (*R*)-(−)-α-deuteriobenzyl bromide, $[\alpha]^{25}_{D}$ −0.737 ± 0.002° (neat, l = 1), 61.4 ± 4% ee,[20] in 78.5% yield.

Reaction of (*R*)-(−)-α-Deuteriobenzyl Bromide with Tetramethyltin. Formation of (*R*)-(−)-α-Deuterioethylbenzene. To a solution of 1.004 g (5.910 mmol) of (*R*)-(−)-α-deuteriobenzyl bromide, $[\alpha]^{25}_{D}$ −0.737 ± 0.002° (neat, l = 1), 61.4 ± 4% ee, and 73 mg (0.096 mmol) of benzylchlorobis(triphenylphosphine)palladium(II) (**1**) in 3 mL of hexamethylphosphoramide under argon was added 1.70 mL (12.3 mmol) of tetramethyltin. After stirring at 63 °C for 20 h, the solution was cooled to 25 °C and 5 mL of water was added. The mixture was extracted with 4 × 5 mL of ether and 2 × 5 mL of pentane. The combined ether and pentane solutions were dried on $MgSO_4$ and concentrated by distillation through a fractionation column to a volume of ca. 2 mL. After performing a vacuum transfer twice to a liquid nitrogen cold trap, 439 mg (70.6%) of (*R*)-(−)-α-deuterioethylbenzene was obtained (pure by GLC) and diluted to a volume of 1 mL by ethylbenzene, $[\alpha]^{25}_{D}$ −0.059 ± 0.003° (neat, l = 1), 8 ± 1% ee.[17]

Racemization of (*R*)-(−)-α-Deuteriobenzyl Bromide. A solution of 1.52 g (8.95 mmol) of (*R*)-(−)-α-deuteriobenzyl bromide, $[\alpha]^{25}_{D}$ −0.572 ± 0.002° (neat, l = 1), 47.7 ± 3% ee and 103 mg (0.136 mmol) of benzylchlorobis(triphenylphosphine)palladium(II) (**1**) in 5 mL of hexamethylphosphoramide was stirred under argon at 65 °C for 20 h. Water (20 mL) was added and the mixture was extracted with ether. The ether solution was washed with water and dried over $MgSO_4$ and the solvent was removed by evaporation. The residue was purified by Kugelrohr distillation to give 1.25 g of α-deuteriobenzyl bromide, $[\alpha]^{25}{}_D$ 0.00. When (*R*)-(−)-α-deuteriobenzyl chloride was used under the same conditions, the recovered chloride was 90.2% racemic.

Benzylchloro-1,2-bis(diphenylphosphinoethane)palladium(II). To a stirred suspension of 3.5 g (5.0 mmol) of dichlorobis(triphenylphosphine)palladium(II) and 4.0 g (10 mmol) of 1,2-bis(diphenylphosphinoethane) in 100 mL of degassed ethanol was added 1.00 g (37.8 mmol) of sodium borohydride, and the suspension was stirred at 25 °C under argon until the gas evolution stopped (4 h). The yellow 1,2-bis(diphenylphosphinoethane)bis(triphenylphosphine)palladium(0),[23] isolated by filtration under argon, was washed with ethanol and dried in vacuo.

To a solution of this complex in 80 mL of degassed benzene under argon was added 3.04 g (24.0 mmol) of benzyl chloride. After being stirred at 25 °C for 36 h, the mixture was filtered and the solvent was removed by evaporation. Pentane-ether (2:1) was added, and the yellow benzylchloro-1,2-bis(diphenylphosphinoethane)palladium(II), isolated by filtration, was washed with pentane and dried in vacuo to give 2.00 g (63.5% based on dichlorobis(triphenylphosphine)palladium(II)) of product: mp 184–186 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.05–6.70 (m, 25 H, phenyls), 3.20 (d of d, J = 4 Hz, 2 H, $PhCH_2$), 2.50 (distorted d, J = 3 Hz, 4 H, $P-CH_2$); ^{13}C NMR ($CDCl_3$) δ 134.434–127.385 (m), 23.163 (s), 21.669 (s), 20.207 (s). Anal. ($C_{33}H_{31}ClP_2Pd$) C, H, Cl: calcd, 5.62; found, 6.17; P: calcd, 9.81; found, 10.94.

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Reactions of Atomic Metal Ions with Alkyl Halides and Alcohols in the Gas Phase

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Abstract: The chemistry of Li^+, Na^+, Fe^+, Co^+, and Ni^+ with alkyl halides and alcohols in the gas phase as elucidated by ion cyclotron resonance spectroscopy is described. The alkali metal ions induce dehydrohalogenation and dehydration of alkyl halides and alcohols, respectively. Reactivity of R-X decreases with increasing $D(R^+-X^-)$ indicating a mechanism involving charge generation at the carbon. A potential energy surface with a barrier associated with such a charge generation is proposed and discussed quantitatively. From halide transfer reactions of RX to alkali metal ions it is deduced that $\Delta H_f{}^\circ{}_{298}$(1-adamantyl cation) = 160.7 ± 3.0 kcal/mol and $\Delta H_f{}^\circ{}_{298}(C_7H_7^+) \leq 215.1 \pm 3.0$ kcal/mol. Fe^+, Co^+, and Ni^+, formed by electron impact on $Fe(CO)_5$, $Co(NO)(CO)_3$, and $Ni(CO)_4$, respectively, dehydrate alcohols and dehydrohalogenate alkyl halides by a mechanism completely different from the alkali metal ion reactions. Oxidative addition of M^+ to RX giving RMX^+ is postulated. In some cases MR^+ and MX^+ products are observed. Limits on several (M^+-X) bond strengths are deduced. It is deduced from observed reactions that the proton affinities of Fe and FeO are ≤203 and ≥227 kcal/mol, respectively. Reactions with the alcohols and alkyl halides of ions other than M^+ formed by electron impact on the carbonyls are also described. Reactions with the neutral metal carbonyls of a number of organic ions formed from the alkyl halides and alcohols are described.

The gas-phase chemistry of simple organic molecules with ions formed by electron impact on metal carbonyls has been the subject of several recent communications from our laboratory.[1-3] We have reported limits on metal to carbon bond strengths in simple transition-metal alkyls.[1] We have also reported direct evidence for metal insertion and β hydrogen shift mechanisms in the reactions of the atomic metal ions with alkyl halides and alcohols.[2] We provide here a more nearly complete description of the ion chemistry observed in gaseous mixtures of $Fe(CO)_5$, $Co(NO)(CO)_3$, and $Ni(CO)_4$ with simple alcohols and alkyl halides.

There have also been several reports on the gas-phase chemistry of alkyl halides with alkali metal ions.[1,4] We report here a mechanistic study of the alkali metal ion induced dehydrohalogenation of alkyl halides and the alkali metal ion induced dehydration of alcohols. An unusual generalization emerges from this study relating reaction rates to thermodynamic properties of the reactants.

The reactions of the transition-metal ions and the alkali-metal ions show superficial similarities. A closer examination reveals marked differences in the mechanism and energetics of the reactions of the two classes of metal ions. We attempt

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