A RE-EXAMINATION OF THE PALLADIUM-CATALYZED CROSS COUPLING
OF ALKYL IODIDES WITH ALKYL GRIGNARD REAGENTS

Kaixu Yuan and William J. Scott[*]

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

Summary: Reaction of primary alkyl halides with Grignard reagents in the presence of
(dppf)Pd(0) or (dppf)PdCl$_2$ leads to the reduction of the halide.

Palladium complexes have been used to catalyze the reactions of a wide variety of
electrophiles, including aryl, acyl, vinyl, allylic, benzylic and acetylenic halides and
pseudohalides.[1] Notably missing from the list are the alkyl electrophiles. It is widely held
that after oxidative-addition of an alkyl electrophile, β-hydride elimination would rapidly
occur.[1] The catalysis of the reactions of alkyl electrophiles is also hampered by the lack of
reactivity of the electrophile toward palladium complexes. By far,the preponderance of
electrophiles amenable to palladium-catalyzed reactions have a π-system either attached or
adjacent to the reacting center. Pearson has shown that low valent palladium species react
with methyl iodide and methyl tosylate at relatively slow rates.[2]

Castle and Widdowson recently reported that 1,1'-bis(diphenylphosphino)ferrocene-
palladium(0) ((dppf)Pd(0)), formed in situ by the reduction of (dppf)PdCl$_2$ with 2 equiv of
DIBAL, efficiently catalyzes the cross-coupling of n-alkyl iodides with Grignard reagents in
ethereal solvents at 0-67°C.[3] For example, reaction of 3-phenyl-1-propylmagnesium bromide (1)
with n-hexyl iodide was shown to give the cross-coupled product, phenylnonane, in 91% isolated
yield. This coupling reaction is noteworthy both because it is the first reported palladium-
catalyzed coupling of an unactivated alkyl electrophile, and because under the reaction
conditions no products of β-hydride elimination were observed. The coupling was said to be
sensitive to steric hindrance in both the electrophile and the nucleophile.[3] Thus, alkyl
Grignard reagents led to higher yields of coupled products than did aryl Grignard reagents.

While studying the ability of various Group 10 metal complexes to catalyze the coupling
of nucleophiles with neopentyl halides, we found that Grignard reagents act to reduce both
hindered and unhindered alkyl halides to the corresponding alkanes in the presence of either
(dppf)Pd(0) or (dppf)PdCl$_2$ in concentrations of 2 to 50 mol%.[4-6] Because of the discrepancy
between our observations and those previously reported, the effect of varying conditions on
the reaction pathway was examined.

The method of generation of the Grignard reagent prior to coupling appears to be an
important factor in the Widdowson reaction.[7] Specifically, after formation of the Grignard
reagent in the presence of excess magnesium, the solution is said to be added, via a (filter
paper covered) filter stick, to a well stirred solution of the alkyl iodide and the palladium
catalyst in THF or diethyl ether at -78°C.[7] Our attempts to repeat this have consistently led
to quenching of the Grignard reagent during the filtration step. Varying the amount of
magnesium used to prepare the reagent also had no effect on the outcome of the reaction.
Ultimately, our Grignard reagents were filtered through scintered glass filters with the aid

Table 1. Reaction of Iododecane with Grignard Reagents.

Entry	Temp °C	Solvent	Catalyst[a]	Grignard Reagent	Conversion	Product Ratio R-H : R(-H) : R-R'		
1	67	THF	None	Ph(CH$_2$)$_3$MgBr (**1**)	96%	92 :	8 :	0
2	67	THF	(dppf)Pd(0)	Ph(CH$_2$)$_3$MgBr (**1**)	100%	100 :	0 :	0
3	67	THF	(dppf)PdCl$_2$	Ph(CH$_2$)$_3$MgBr (**1**)	100%	94 :	6 :	0
4	25	Et$_2$O	None	Ph(CH$_2$)$_3$MgBr (**1**)	10%	99 :	1 :	0
5	25	Et$_2$O	(dppf)Pd(0)	Ph(CH$_2$)$_3$MgBr (**1**)	83%	85 :	15 :	0
6	25	Et$_2$O	(dppf)PdCl$_2$	Ph(CH$_2$)$_3$MgBr (**1**)	66%	96 :	4 :	0
7	0	THF	(dppf)Pd(0)	MeMgCl	100%	21 :	77 :	2
8	0	THF	(dppf)Pd(0)	PhMgBr	100%	57 :	19 :	24

a) When catalyst was added, 5 mol% was used. (dppf)Pd(0) was prepared as described in Ref 3.

of dry celite directly into dry storage containers and titrated[8] prior to use. Standard syringe techniques were used for transfer of the reagents.
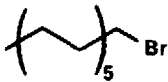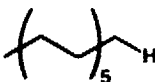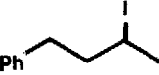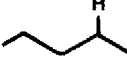
In THF, the reduction of iododecane with **1** appears not to require palladium catalysis (Table 1, entries 1-3). No cross-coupling was observed with or without palladium. Grignard reagents have been used to reduce alkyl halides by a transmetallation/protonolysis mechanism.[9] A similar reaction would appear to be operative in this case.[10]

Iododecane is also reduced by **1** in diethyl ether (Table 1, entries 4-6). In this solvent either (dppf)Pd(0) or (dppf)PdCl$_2$ is required for reaction to occur. Catalyst concentration effects[11] and the lack of reduction in the absence of palladium suggest that in ether the palladium must play a role in the reduction mechanism.[10]

The product distribution varies considerably depending on the Grignard reagent employed. Thus, while n-alkyl Grignard reagents led to reduction of iododecane, methylmagnesium chloride predominantly causes elimination, giving 1-decene in 77% yield (Table 1, entry 7). Phenyl-magnesium bromide afforded decane in 56% yield along with moderate amounts of 1-decene and the coupling product, 1-phenyldecane (Table 1, entry 8). Notably, coupling proved to be a minor pathway regardless of the Grignard reagent employed.

Attempts to facilitate coupling by addition of catalytic or stoichiometric amounts of a cocatalyst met with little success. Neither addition of Fe(acac)$_3$,[12] nor formation of organozinc reagents[13] using ZnCl$_2$, ZnBr$_2$, or ZnI$_2$, acted to afford coupled products in the presence of (dppf)Pd(0). Addition of CuI in either catalytic or stoichiometric amounts gave a 2:1 ratio of coupled to reduced products.[14] The palladium catalyst actually appears to hinder the Cu(I)-catalyzed Gilman-coupling reaction of iododecane with **1**. Reaction of iododecane

Table 2. Reaction of Alkyl Halides with EtMgBr and 1-2 mol% (dppf)PdCl$_2$.

Entry	Alkyl Halide	Alkane	Isolated Yield (%)[a]
1			76
2			76 (100)
3			64 (100)
4			80 (100)
5			-- (~50)[b]

a) Numbers in parentheses refer to GC yields obtained from separate reactions.
b) Butylbenzene was obtained contaminated with approximately 50% of a mixture of 4-phenyl-1-butene and E- and Z-1-phenyl-2-butene.

with **1** in the presence of catalytic CuI and in the absence of palladium catalysts afforded quantative yields of 1-phenyltridecane.

The experiments shown in Table 2 suggest that the reduction is a general process. Because little difference is seen between the reactivity of (dppf)Pd(0) and (dppf)PdCl$_2$ (Table 1), the catalyst was not pre-reduced with DIBAL for these experiments. Ethylmagnesium bromide was used as the Grignard reagent in order to simplify purification of the product. Treatment of a primary halide with ethylmagnesium bromide in THF at 67°C in the presence of 1-2 mol% (dppf)PdCl$_2$ led to the corresponding, somewhat volatile alkanes in good to moderate isolated yields (Table 2).[5] In separate reactions, yields from primary halides as determined by gas chromatography were found to be quantitative. Hindered and unhindered alkyl halides are reduced with equal facility, as are alkyl chlorides. Elimination pathways, where available, appear to become competitive with reduction for more highly substituted halides. Thus, 3-iodo-1-phenylbutane (**9**) afforded butylbenzene (**10**) in approximately 50% yield along with a mixture of alkenes predominating in 4-phenyl-1-butene (Table 2, entry 5).

In conclusion, in our hands (dppf)Pd(0) and (dppf)PdCl$_2$ have not acted as efficient catalysts for the coupling of alkyl halides with Grignard reagents. Reduction products are most commonly encountered and β-hydride elimination occurs in some cases. Reactivity toward

coupling appears to favor aryl Grignard reagents over alkyl. The experimental factors required to suppress the reduction observed in our laboratories, and allow the reported coupling[3] to predominate are not yet obvious.[6]

REFERENCES

1. Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, (1987).

2. Pearson, R.G.; Figdore, P.E. J. Am. Chem. Soc. 1980, 102, 1541-1547.

3. Castle, P.L.; Widdowson, D.A. Tetrahedron Lett. 1986, 27, 6013-6016.

4. Presented in part at the Third Chemical Congress of North America, 7 June 1988, Toronto, Canada, ORCN 158.

5. **General Experimental Procedure**: To 0.015 g (0.02 mmol, 2.0 mol%) of $(dppf)PdCl_2$ which had been placed under Ar using 2 cycles of an evacuate/quench protocol and cooled to $-78^{\circ}C$ was added 8 mL of dry THF, followed by 1.00 mmol of alkyl iodide, 1.5-4.0 mmol of ethylmagnesium bromide (2.5 $\underline{M}$ in THF), and then an additional 2 mL of THF. This mixture was allowed to warm to the reaction temperature over 4-6 h and maintained at that temperature for 8-12 h. The resulting black slurry was cooled to room temperature, diluted with 15 mL of pentane, and washed with 20 mL of water. The aqueous layer was back-extracted with 15 mL of pentane and the combined organics were sequentially washed with 10-15 x 20 mL H_2O, 1 x 20 mL 1% HCl, 2 x 20 mL H_2O, and 2 x 20 mL of a conc. NaCl solution. The resulting solution was dried over anh $MgSO_4$ and filtered through a small pad of silica gel. Solvent was removed by distillation using a 100 cm Vigeraux column and the remaining oil was purified by bulb-to-bulb distillation or by spinning band distillation to give the final product as a clear colorless oil. Reactions run for GC analysis were similar, except 0.700 mmol of bibenzyl was used as an internal standard.

6. Professor Widdowson has also encountered some difficulty in repeating the coupling reaction.[7] Recent results from his laboratories indicate that the reaction produces alkane/alkene mixtures in agreement with our findings.

7. Widdowson, D.A., private communication.

8. Watson, S.C.; Eastham, J.F. J. Organometal. Chem. 1967, 9, 167-168.

9. Bryce-Smith, D.; Wakefield, B.J.; Blues, E.T. Proc. Chem. Soc. 1963, 219.

10. The results of studies on the mechanism of the reduction of alkyl halides in the presence and absence of palladium catalysts will reported shortly.

11. Yuan, K.; Scott, W.J., unpublished results.

12. Neumann, S.M.; Kochi, J.K. J. Org. Chem. 1975, 40, 599-606. Kochi, J.K.; Smith, R.S. J. Org. Chem. 1976, 41, 502-509.

13. Negishi, E.-i. Acc. Chem. Res. 1982, 15, 340-348.

14. Posner, G.H. Org. React. (N.Y.) 1975, 22, 253-400.

(Received in USA 13 January 1989)