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A STUDY OF CROSS COUPLING REACTIONS BETWEEN HALIDES AND ANIONIC MANGANESE, IRON, AND COBALT ALKYLS

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A new method for the selective formation of carbon-carbon bonds between unlike groups which involves the reaction of anionic organocopper reagents with organic halides has been developed previously in these laboratories (1,2) and applied (3,4) as a key step in certain syntheses, e.g., of the C_{18}-juvenile hormone from Cecropia (4). The general formulation of the coupling process is outlined in equation 1. The coupling

$$\text{RHal} + \text{R}'_2\text{CuLi} \longrightarrow \text{R-R}' + \text{LiHal} + \text{R}'\text{Cu} \qquad \text{eq. 1}$$

is especially effective as applied to vinylic, aromatic, and primary alkyl halides. In view of the utility of the method and the interesting question of mechanism, it seemed important to examine the possible application of similar reagents containing other metals of the first transition series to cross coupling reactions with halides. The results of such an investigation are summarized herein.

Complex anions of manganese of type R_3MnLi (5,6) which are analogous to the copper reagents R_2CuLi and which possess at least comparable thermal stability appeared to be promising candidates for study. The reagents having R = methyl, ethyl, or n-butyl are readily prepared from manganous bromide and 3 equiv. of the appropriate alkyllithium in ether (under nitrogen), and they are sufficiently stable for use in situ at 0° (5,6).

It was found that the trimethylmanganeselithium reagent did indeed undergo the same type of coupling reaction as the dimethylcopperlithium reagent with a variety of halide substrates. Table I records the experimental results obtained with the reagent $(CH_3)_3MnLi$ (7) in excess (5 moles per mole of halide). The most efficient coupling occurred with halide substrates of the vinylic and allylic type. Only moderate yields of cross coupling product were obtained in the case of the indicated primary alkyl iodide, aryl iodide, and cyclopropyl bromide. Secondary and tertiary alkyl halides and organic chlorides in general do not appear to be satisfactory substrates, at least under the standard conditions used with ether as solvent. The major by-products from the reaction of halides with trimethylmanganeselithium appear to result from intermediates derived by metal-halogen replacement.

Tri-n-butyl- and triethylmanganeselithium (7) were considerably less effective as cross coupling reagents than the trimethyl analog (even when used in excess) and appeared to function well only with certain vinylic bromides or iodides (Table II). In other cases the main reaction product was found to correspond either to (1) replacement of Hal by H, (2) elimination of H-Hal (primary iodide), or (3) symmetrical coupling of R-Hal (allylic or benzylic bromide); again, each of these products might be derived from an intermediate in which manganese has replaced halogen.

An investigation was likewise made of the behavior of the reagents prepared from reaction in ether of 3 equiv. of methyllithium with 1 equiv. of ferrous iodide (-20°) or cobaltous iodide (-20°) (nitrogen atmosphere). Both reagents were brown-black in color and exhibited appreciable decomposition upon storage at 0° for several hours. The results obtained with the organoiron reagent, some of which are summarized in Table III, are generally similar to those found with trimethylmanganeselithium, although the rates of reaction of the iron reagent with halides are considerably faster than those observed with the manganese reagent. Trimethylcobaltlithium reagent also appeared to be very reactive toward halides. However, the predominant course of reaction with most of the halides listed in Table III was *via* metal halogen replacement; a predominance of cross coupling was only observed with vinylic bromides or iodides. The reagents prepared from *n*-butyllithium and ferrous iodide or cobaltous iodide were uniformly ineffective in causing cross coupling with the halides cited in the Tables.

Some conclusions follow from the above, and earlier (1,2), results. First of all, the cross coupling reaction originally observed with copper reagents (1,2) is not unique to these reagents, but can to various degrees be observed with manganese, iron, and cobalt analogs. Second, the copper reagents of type R_2CuLi are superior in cross coupling reactions to the manganese, iron, and cobalt reagents. Third, the latter reagents of type R_3MnLi become much less effective in cross coupling as R is changed from methyl to *n*-alkyl.

Unfortunately, the present results do not allow a distinction between the most reasonable mechanistic possibilities for the initial reaction between these anionic transition metal reagents and organic halides. These are (to illustrate with the copper reagent) (a) electron transfer (equations 2, 3) and (b) nucleophilic replacement of halogen by metal (either with C-Hal 'insertion' or S_N2 displacement at C) (equation 4) (8). It

$$\mathrm{RHal} + \mathrm{R'_2CuLi} \longrightarrow \mathrm{R\cdot} \quad \mathrm{R'_2Cu\cdot} \quad \mathrm{Li^+Hal^-} \qquad \text{eq. 2}$$

$$\mathrm{RHal} + \mathrm{R'_2CuLi} \longrightarrow \mathrm{R\cdot} \quad \mathrm{R'\cdot} \quad \mathrm{R'Cu} \quad \mathrm{Li^+Hal^-} \qquad \text{eq. 3}$$

$$\mathrm{RHal} + \mathrm{R'_2CuLi} \longrightarrow \mathrm{RCuR'_2} \quad \mathrm{Li^+Hal^-} \qquad \text{eq. 4}$$

would seem likely, however, that the critical property of the copper, manganese, iron, and cobalt reagents which permits rapid reaction with Csp^2 and Csp^3 halides is the availability of one or two non-bonding electrons from a high energy metallic *d*-orbital. Considering, for example, the unassociated form of the copper complex $R_2Cu^- Li^+$, with sp_x bonding to carbon, all five 3d orbitals will be filled. The orbital d_{z^2} will be highest in energy and also will be vulnerable sterically to electrophilic attack on the metal (in the Z direction). In this regard it is noteworthy that trimethylzinclithium (9) has been found to be less reactive than the copper, manganese, iron, or cobalt reagents described above in coupling with *trans*-1-bromo-2-phenylethylene (10). In addition, this anionic zinc reagent leads to products which are more typical of alkyllithium reagents than the anionic alkyl transition metal reagents. Only preliminary studies have been carried out with the 3 : 1 reagents derived from methyllithium and nickel(II) iodide or chromous iodide. These reagents appear to be comparable in reactivity with the other transition metal analogs in coupling with *trans*-1-bromo-2-phenylethylene (10).

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Table I. Methylation with Trimethylmanganeselithium* in Ether

Halide	Temp.	Time	Product (% Yield)
1-Iododecane	0°	21 hr.	*n*-Undecane (55[a,c])
Iodocyclohexane	0°	21 hr.	Methylcyclohexane (10[b,d])
3-Bromocyclohexene	-20°	1 hr.	3-Methylcyclohexene (75[b])
Iodobenzene	0°	48 hr.	Toluene (50[b,e])
trans-1-Iodo-1-nonene	0°	1 hr.	*trans*-2-Decene (82[a])
trans-1-Bromo-2-phenylethylene	0°	46 hr.	*trans*-1-Phenylpropene (82[a])
1-Bromocyclohexene	25°	18 hr.	1-Methylcyclohexene (65[b])
7,7-Dibromonorcarane	0°	20 hr.	7,7-Dimethylnorcarane (50[b])

*Five moles of the reagent per mole of halide.

[a] Yield of isolated product. [b] Yield by v.p.c. analysis. [c] *n*-Decane and 1-decene are the by-products. [d] 40% cyclohexene, 10% bicyclohexyl. [e] 20% biphenyl.

Table II. Reaction of Halides with Tributylmanganeselithium* in Ether

Halide	Temp.	Time	Product (% Yield)
1-Iododecane	0°	20 hr.	1-Decene (90)
Iodocyclohexane	0°, 25°	16 hr., 9 hr.	Cyclohexane (a) *n*-Butylcyclohexane (10)
3-Bromocyclohexene	-20°	1 hr.	3,3'-Bicyclohexenyl (a) 3-*n*-Butylcyclohexene (10)
Iodobenzene	0°	48 hr.	Benzene (70), *n*-Butylbenzene (30)
trans-1-Iodo-1-nonene	-78°, -20°	2 hr., 0.5 hr.	*trans*-5-Tridecene (30) 1-Nonene (40)
trans-1-Bromo-2-phenylethylene	0°, 25°	1 hr., 3 hr.	*trans*-1-Phenylhexene (65)

*Five moles of reagent per mole of halide.

(a) Major product.

Table III. Methylation with Trimethylironlithium* in Ether

Halide	Temp.	Time	Product (% Yield)
1-Iododecane	-78°	3 hr.	*n*-Undecane (2[b,c])
Iodocyclohexane	-20°	1 hr.	Methylcyclohexane (10[b,d])
3-Bromocyclohexene	-20°	1 hr.	3-Methylcyclohexene (50[b])
Iodobenzene	-78°	3 hr.	Toluene (50[b,e])
trans-1-Iodo-1-nonene	-78°	1 hr.	*trans*-2-Decene (90[a])
trans-1-Bromo-2-phenylethylene	-78°	1.5 hr.	*trans*-1-Phenylpropene (83[a])
1-Bromocyclohexene	-78°, 0°	3, 12 hr.	1-Methylcyclohexene (75[b])
7,7-Dibromonorcarane	-78°, 0°	4, 12 hr.	7,7-Dimethylnorcarane (65[b,f])

*Five moles of reagent per mole of halide.

[a] Yield of isolated product. [b] Yield by v.p.c. analysis. [c] 66% 1-decene. [d] Mainly cyclohexene. [e] Methyliodide added to reaction mixture after all reactant halide had disappeared; 20% biphenyl. [f] 15% *exo*-7-methylnorcarane.

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