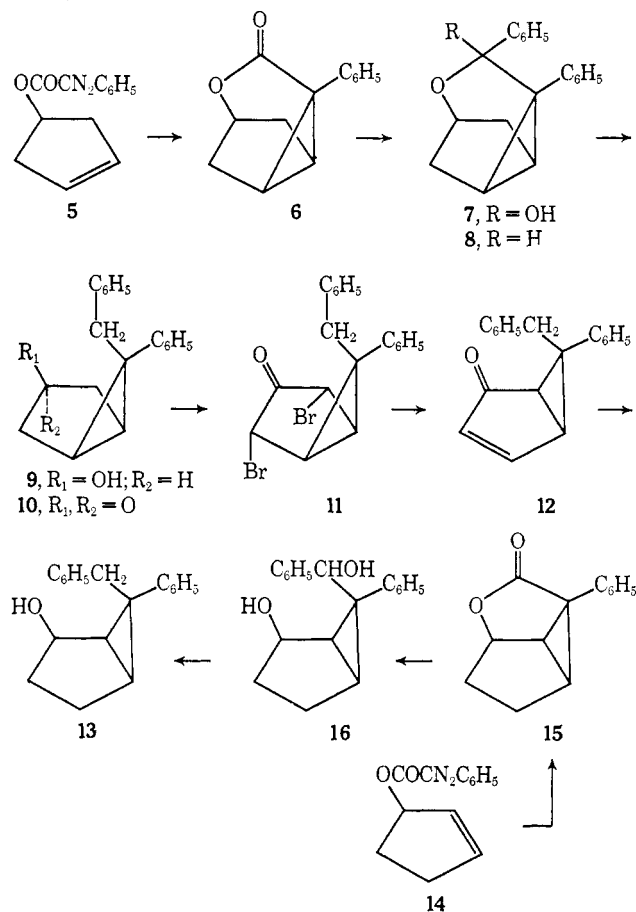


13, mp 104–106°, with lithium tri-*t*-butoxyaluminum hydride. This alcohol was synthesized independently by an analogous route, involving cyclization of the diazo ester **14** derived from cyclopent-2-en-1-ol to lactone **15**, ν 1760 cm^{-1} , reaction with phenyllithium, LiAlH_4 reduction to diol **16**, mp 146–148°, and finally sodium–ammonia reduction to **13**. The samples of **13** produced by these two routes showed no melting point depression on admixture and had identical infrared and nmr spectra.

In agreement with the configurations assigned to these compounds is the downfield shift of the benzylic methylene group in the nmr spectra of alcohols **9** (δ 3.21) and **13** (δ 3.40) relative to its position in ketones **10** (δ 2.85) and **12** (δ 3.05).

The inversion of configuration at migrating carbon in this 1,4-sigmatropic shift provides yet another example in a previously unstudied system of the



predictive powers of orbital symmetry correlations.

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Carbon–Carbon Bond Formation by Selective Coupling of *n*-Alkylcopper Reagents with Organic Halides

Sir:

Two new methods for carbon–carbon bond formation between unlike groups derived from an organic

halide and an organo–transition metal derivative have recently been described.^{1,2} One of these is generally effective for allyl–nonallyl coupling and involves the use of π -allylhalonickel complexes;¹ the other utilizes as reagent the product from the interaction of an alkyl–lithium compound with cuprous iodide in a molar ratio 2:1.^{3,4} The copper method was shown to have broad applicability for a wide variety of halides of the $\text{C}(\text{sp}^2)$ –Hal as well as $\text{C}(\text{sp}^3)$ –Hal type, using the reagent derived from methylolithium. This communication is concerned with the extension of the coupling reaction to *n*-alkylcopper reagents which demonstrates generality for the primary alkyl organometallic class.

Addition of *n*-butyllithium (Foote Mineral Co., hexane solution) to an ethereal suspension of cuprous iodide⁵ at -20° leads to formation of a dark insoluble product at a 1:1 molar ratio which by analogy with previous work probably corresponds to $(\text{RCu})_n$. The precipitate dissolves upon addition of a second equivalent of *n*-butyllithium to give a brown-black solution probably containing a solvated complex species; both this reagent (arbitrarily described below as R_2CuLi) and the insoluble 1:1 mixture respond negatively in the test for free alkylolithium using Michler's ketone.⁶ In the butyl series, as found previously for the methyl series,² R_2CuLi is considerably more reactive toward organic halides than is $(\text{RCu})_n$ and also much more efficient in cross-coupling. Dark 2:1 complexes of type R_2CuLi have also been prepared from ethyllithium and *n*-heptyllithium in a manner analogous to the butyl case. Since the reactions of these three reagents with halides have been found to be closely similar, one case, $\text{R} = n$ -butyl, was selected for intensive study.

The reaction of lithium di-*n*-butyl- or diethylcopper⁷ reagents (ca. 0.25 *M*, 5 molar equiv) with a number of halides in ether as solvent led to efficient cross-coupling as indicated, for example, by eq 1–11, which also summarize experimental conditions.⁸

In general, the lithium di-*n*-alkylcopper reagents react more rapidly with halides than does lithium dimethylcopper, but they are also less stable thermally. They are also more apt to produce halogen–copper exchange as a side reaction (*i.e.*, $\text{R-Hal} \rightarrow \text{R-Cu}$) than is lithium dimethylcopper. Such exchange, especially serious with the starting halides of eq 8, 9, and 11, can be nullified by a subsequent addition to the reaction mixture of an excess of the alkyl halide corresponding to the *n*-alkylcopper reagent. Without such treatment the

(1) E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).

(2) E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967).

(3) H. Gilman, R. G. Jones, and L. A. Woods, *J. Org. Chem.*, **17**, 1630 (1952).

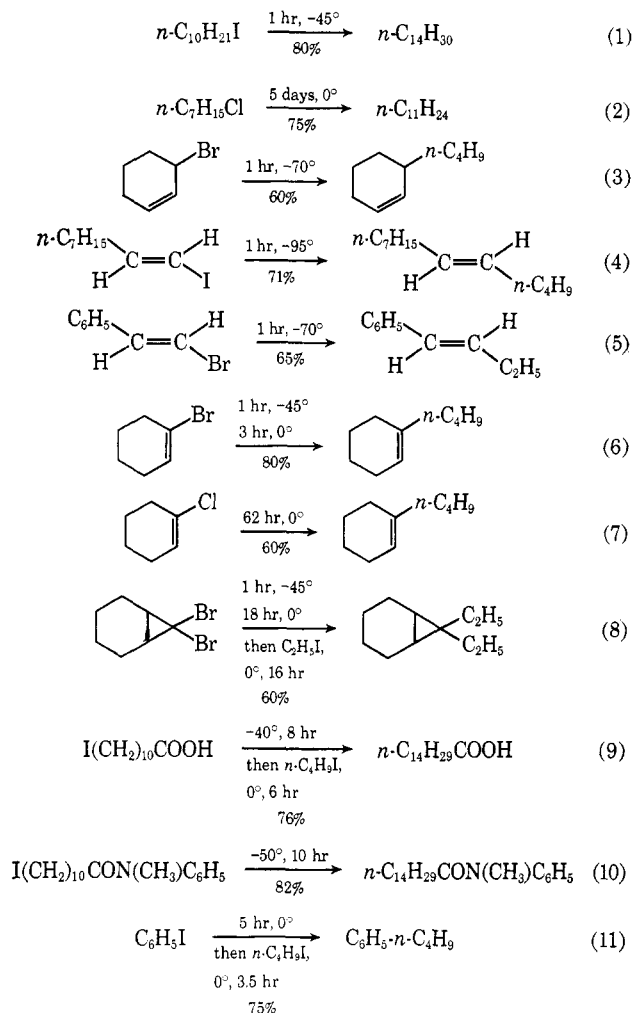
(4) H. Gilman and J. M. Straley, *Rec. Trav. Chim.*, **55**, 821 (1936).

(5) All reactions involving organometallic reagents were carried out with the usual precautions for rigorous exclusion of air and moisture.

(6) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(7) The use of this designation is not intended to carry structural implications. One intriguing possibility is that the dimeric species $[\text{R}_2\text{Cu}_2\text{Li}_2]$ might predominate because it can adopt a tetrahedral structure analogous to that of $[\text{CH}_3\text{Li}]_2$, with two Li being replaced by two Cu (for $[\text{CH}_3\text{Li}]_2$ see E. Weiss and E. A. C. Lucken, *J. Organometal. Chem.*, **2**, 197 (1964)). If the dominant species is the monomeric complex $[\text{R}_2\text{CuLi}]$, a structure analogous to $[\text{C}_2\text{H}_5\text{Li}]_2$ (H. Dietrich, *Acta Cryst.*, **16**, 681 (1963)) would appear to be plausible. Clearly, physical studies on these copper reagents in solution are in order.

(8) In all cases products were analyzed by gas chromatography (gc), isolated, and characterized. Previously described compounds were compared by gc and nmr and infrared spectroscopy with authentic samples. New compounds were purified by gc and characterized by nmr, infrared, and mass spectroscopy.



yields of the products shown in (8) and (11) were *ca.* 10 and 30%, respectively. The following by-products were observed in the above reactions: cyclohexene (10%) in reaction 3, 1-nonene (15%) and 8,10-octadecadiene (5%) in reaction 4, styrene (15%) and *trans*-1,4-diphenylbutadiene (10%) in reaction 5, 7-ethylnorcaradiene (20%) in reaction 8, and benzene (20%) in reaction 11. Clearly, the principal side reaction in these cases is due to replacement of halogen by metal followed by protonation during the usual aqueous work-up. This side reaction may become dominant as, for example, with α -bromo ketones. Elimination may also be a major reaction pathway as with cyclohexyl iodide, which affords only cyclohexene. In general, the selection of experimental conditions is more critical with *n*-alkylcopper reagents than with lithium dimethylcopper as a result of these complications.⁹

There also appears to be a marked effect of temperature on the reactions of lithium dialkylcopper reagents, and in many cases an optimum point can be located, above and below which yields of cross-coupling product

(9) Significant solvent effects have been noted. Whereas in ether as solvent benzyl bromide reacts with lithium di-*n*-butylcopper to give mainly 1,2-diphenylethane (*ca.* 60%) and lesser amounts of *n*-amylbenzene (30%), in tetrahydrofuran these products are generated in yields of 60 and 10%, respectively. On the other hand, the yields of cross-coupling product from the reaction of lithium di-*n*-butylcopper with some halides, *e.g.*, certain vinylic bromides, are higher when ether or a hydrocarbon rather than tetrahydrofuran is used as solvent. The reactions of lithium di-*n*-butylcopper have been observed to proceed more rapidly in tetrahydrofuran than in ether.

diminish. In our experience the optimum temperature tends to increase (within the over-all range -95 to 0°) with decreasing reactivity of the halide, approximately in the order $>\text{C}=\text{CH}(\text{I}, \text{Br})$, $\text{RCH}_2\text{CH}_2\text{I}$, $>\text{C}=\text{CR}(\text{I}, \text{Br})$, $>\text{C}=\text{CRCl}$, $\text{RCH}_2\text{CH}_2\text{Cl}$. Secondary halides are much less suited to coupling with lithium di-*n*-butylcopper than are primary halides. For example, reaction of this copper reagent with cyclohexyl iodide either in ether or tetrahydrofuran gave no detectable *n*-butylcyclohexane but mainly cyclohexene.

It should be noted that *n*-butyllithium (or ethyllithium) is a totally unsatisfactory reagent for most of the transformations discussed above, since it exhibits a much greater tendency to cause proton abstraction leading to 1,2 elimination and metal-halogen exchange.¹⁰ It should also be pointed out that the copper reagents allow the use of substrates containing functional groups such as COOH and CONR_2 in unprotected form (see eq 9 and 10) and also can lead to stereospecific coupling processes (see eq 4 and 5). This latter property of the cross-coupling reaction has been used effectively in stereospecific syntheses of farnesol¹¹ and insect juvenile hormone.¹²

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health. We are indebted to Dr. Isao Kuwajima for assistance with some of the experiments.

(10) See, for example, H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, **63**, 1441 (1941); H. Gilman, W. Langham, and F. W. Moore, *ibid.*, **62**, 2327 (1940); D. E. Applequist and D. F. O'Brien, *ibid.*, **85**, 743 (1963).

(11) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *ibid.*, **89**, 4245 (1967).

(12) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968).

E. J. Corey, G. H. Posner

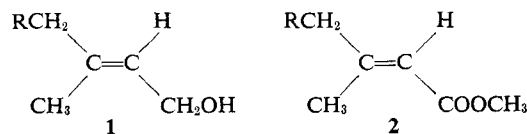
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New Methods for the Oxidation of Aldehydes to Carboxylic Acids and Esters

Sir:

In connection with a synthesis of insect juvenile hormone which has been under study in these laboratories,¹ it was desirable to devise a simple method for the stereospecific conversion **1** \rightarrow **2** under mild condi-



tions. This communication describes an efficient and useful oxidation process *via* aldehyde intermediates which has been developed for this purpose and another method which permits the oxidation of aldehydes to carboxylic acids in neutral or slightly basic media.

Manganese dioxide (active²) is an effective and selective oxidizing agent which cleanly converts primary allylic alcohols to conjugated aldehydes^{3a} without sig-

(1) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).

(2) (a) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948); (b) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).