This Week's Citation Classic

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House H O, Respess W L & Whitesides G M. The chemistry of carbanions. XII. The role of copper in the conjugate addition of organometallic reagents.
J. Org. Chem. **31:**312841, 1966.
[Dept. Chemistry, Massachusetts Inst. Technol., Cambridge, MA]

Preformed methylcopper derivatives have been found to undergo selective conjugate addition to á,âunsaturated carbonyl compounds. The major reaction path followed in these conjugate additions does not involve a cyclic sixcentered species formed from the two reactants. [The *SCI*® indicates that this paper has been cited over 245 times since 1966.]

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"Forty years ago small amounts of added copper compounds were found to favor the addition of Grignard reagents to the âcarbon atom (called conjugate addition) rather than the carbonyl group (called 1,2addition, the normal mode of reaction) of á,âunsaturated carbonyl compounds. This discovery by Kharasch and Tawney[1] was used extensively by chemists during the next 25 years to enhance the amount of the conjugate adduct formed from Grignard reagents and unsaturated carbonyl compounds. Our initial study[2] of the factors influencing the proportions of 1,2addition and conjugate addition convinced us that the effect of added copper derivatives was much greater than effects from other changes in experimental conditions.

"In the earlier phases of the work reported in the paper being cited, we demonstrated that added copper compounds accelerated conjugate addition rather than inhibiting 1,2addition. These observations suggested that the actual reactant was an organocopper compound and led us to prepare solutions containing several derivatives of the insoluble methylcopper including $CH_3CuP(Bun)_3$ and $Li(CH_3)_2Cu$. As anticipated, these organocopper derivatives proved to be very reactive in conjugate addition to unsaturated carbonyl compounds. We were also delighted to find that these copper reagents reacted relatively slowly with nonconjugated ketones and failed to react at all with nonconjugated esters and nitriles. Consequently, when these organocopper reagents were used in stoichiometric quantities, they exhibited high chemoselectivity for conjugate addition even in molecules containing other functional groups that would have reacted with Grignard reagents.

"Other chemists were promptly attracted by the chemoselectivity offered by organocopper reagents and papers describing various applications of these reagents in chemical syntheses were published from many laboratories. Within five years a sufficient volume of work concerned with organocopper reagents had been published to justify the preparation of an *Organic Reactions* chapter reviewing the subject.[3] Publications describing various applications of organocopper reagents in chemical syntheses have continued to the present. These reagents now occupy a secure spot among the collection of tools used by the chemist for the syntheses of organic molecules.

"There are at least three reasons why this paper has been consulted and cited by others using organocopper reagents. (1) It was the first paper to recognize and demonstrate the advantage of using preformed organocopper reagents rather than coppercatalyzed Grignard reactions to effect conjugate additions. (2) The paper includes adequate experimental detail concerning the preparation of precursors and organocopper reagents and the use of these reagents. Thus, it is a good 'howtodoit' reference. (3) The paper includes spectroscopic information bearing on the structures of the organocopper reagents and experimental data relating to the stereochemical outcome and reaction mechanism of the conjugate addition process. Although much additional information about these topics has been obtained in the past 15 years, this paper still provides a good starting point for someone interested in pursuing questions of structure or reaction mechanism."

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1. **Kharasch M S & Tawney P O.** Factors determining the course and mechanisms of Grignard reactions. II. The effect of metallic compounds on the reaction between isophorone and methylmagnesium bromide.*J. Amer. Chem. Soc.* **63**:230816,1941.
2. **House H O, Traficante D D & Evans R A.** The chemistry of carbanions. II. The reaction of organomagnesium compounds with á,ß-unsaturated ketones. *J. Org. Chem.* **28**:34855, 1963.
3. **Posner G H.** Conjugate addition reactions of organocopper reagents. *Organic reactions.* New York: Wiley, 1972.p.1113