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STOICHIOMETRIC VERSUS CATALYTIC USE OF COPPER(I) SALTS IN THE SYNTHETIC
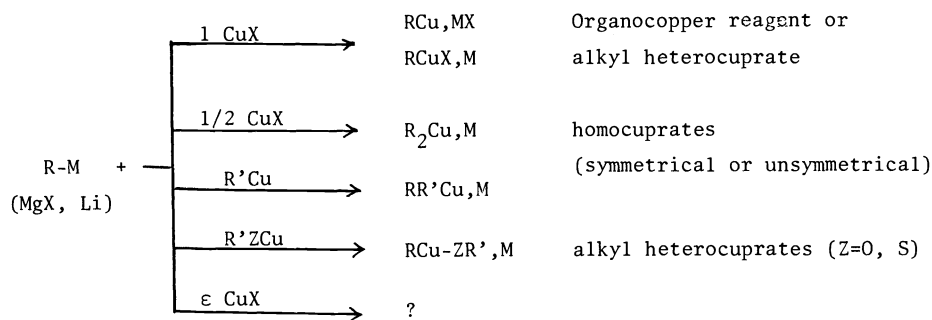USE OF MAIN GROUP ORGANOMETALLICS

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Abstract- We review some applications of copper derivatives as synthetic
tools: stoichiometric organocopper reagents and organomagnesium derivatives
in the presence of catalytic amounts of copper salts are able to give a
regioselective addition on to acetylenic substrates and to alkylate alkyl
or vinyl halides, bromohydrines, their tosylates and carboxylates, and
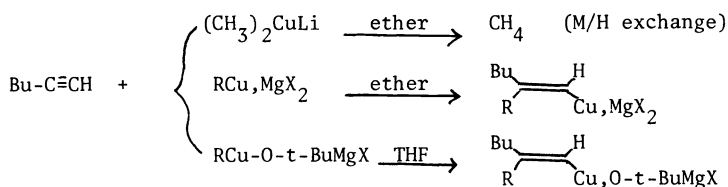a large variety of allylic substrates.

INTRODUCTION

Organocopper chemistry has been developping tremendously these last ten years, mainly because
of the selectivity and the velocity of the reaction processes, even at low temperatures, two
important factors to be considered when dealing with complex and fragile molecules. I shall
endeavour to compare the possible uses of organocopper reagents, organocuprate reagents and
Grignards in the presence of a catalytic amount of Cu^I salt, first in the field of addition
to unactivated $C \equiv C$ bonds, and second, in the field of alkylation of various electrophiles:
organic halides, acetates, ethers... These reagents allow reactions that Grignard alone would
not be able to promote, but many parameters have to be settled accurately: temperature,
solvent, presence of sulfur-, nitrogen-, phosphorous-, halogen-derived ligands. A clear survey
of the respective influence of these factors cannot be drawn by this time.
Organocopper species are derived, in practice, from Organomagnesium- or lithium reagents:

| R-M + (MgX, Li)		
1 CuX →	RCu,MX	Organocopper reagent or
	RCuX,M	alkyl heterocuprate
1/2 CuX →	R_2Cu,M	homocuprates
R'Cu →	RR'Cu,M	(symmetrical or unsymmetrical)
R'ZCu →	RCu-ZR',M	alkyl heterocuprates (Z=O, S)
ε CuX →	?	

I ADDITION TO UNSATURATED C=C BONDS

We have shown, a few years ago, that organocopper reagents, prepared from organomagnesium
compounds, add to terminal alkynes in ether, whereas lithium dimethylcuprate gives a metal/
hydrogen exchange(1). This reaction has been recently extended to the case of magnesium and
lithium homo- and heterocuprates in THF as a solvent(2,3).

$$Bu-C \equiv CH + \begin{cases} (CH_3)_2CuLi \xrightarrow{\text{ether}} CH_4 \quad \text{(M/H exchange)} \\ RCu,MgX_2 \xrightarrow{\text{ether}} \underset{R}{\overset{Bu}{>}} = \underset{Cu,MgX_2}{\overset{H}{<}} \\ RCu-O-t-BuMgX \xrightarrow{\text{THF}} \underset{R}{\overset{Bu}{>}} = \underset{Cu,O-t-BuMgX}{\overset{H}{<}} \end{cases}$$

With acetylene itself, we have shown that organocopper regents prepared either from Grignards
or organolithium compounds, give the addition(4). So do also lithium homo- and hetero-alkyl
cuprates in ether, whatever the lower P_K value of this hydrocarbon which might have favoured

a metal-hydrogen exchange. More recently, Vermeer et al. have extended this reaction to the case of magnesium homo- and hetero-alkylcuprates in THF(2).
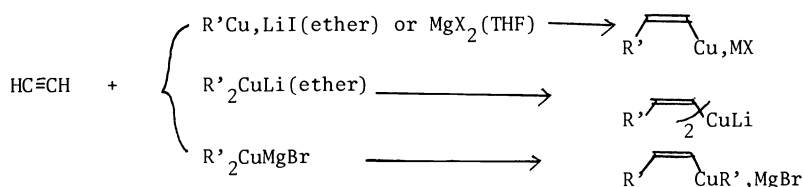
These reactions lead to a syn, regioselective addition which made us hope for an easy transfer of the ethylenic synthon with retension of configuration, when the low thermal stability of these species can be overcome. For example, we have studied the following transformations(1):
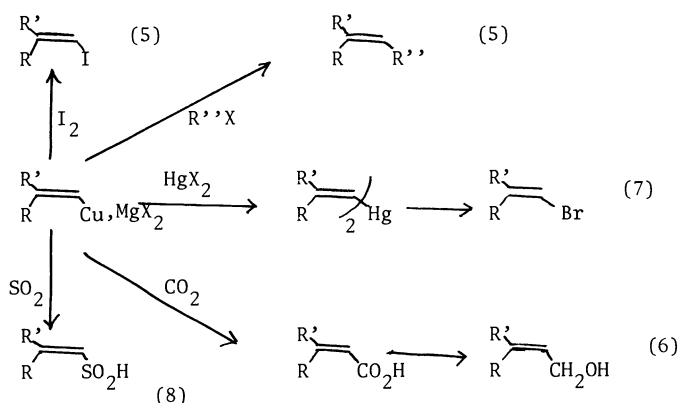

The conjugate addition of vinylheterocuprates to propiolic ester represents a rapid access to conjugated diene structures. Our efforts to obtain the Cu(I) catalysed addition of Grignards to alkynes has met with little success so far (40% maximum),but it occurs indeed. When the alkyl chain of an alkyne bears a functionnality, this latter can interact with the reagent and modifies the regioselectivity. Thus, in the homopropargylic series, when a sulfur atom is two carbon apart from the yne moiety, and maintained in a cis relationship by an appropriate C=C double bond, only the linear (L) product is formed, whereas, in the trans case, the branched (B) product accounts for the non-participation of the hetero atom. The free rotating C-C single bond, in a homopropargyl sulfide, leads to a mixture of both processes(9):
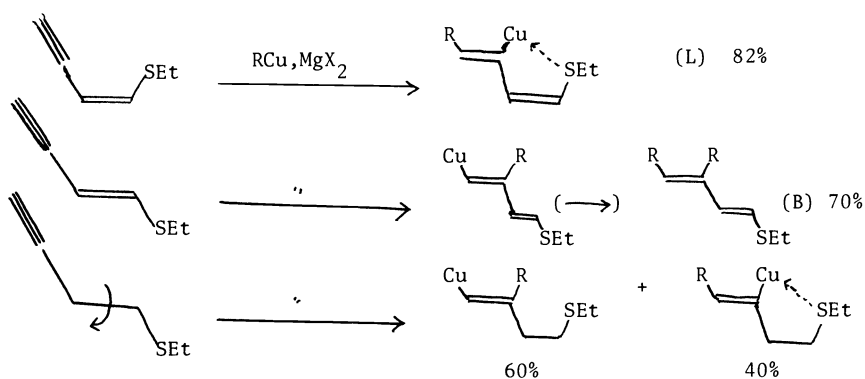

Coordination of sulfur to copper is able to revert the regioselectivity of addition. A similar effect is observed with oxygen instead of sulfur, but now the nature of the solvent is of major importance: homopropargyl ethers give a "linear" product in ether, and a "branched" one in THF. In the field of catalysis, Duboudin and Jousseaume(10) have shown that propargylic alcohols add saturated Grignard reagents only in the presence of catalytic amounts of Cu(I) salts; but a totally different regio- and stereo-selectivity is observed, as compared with the stoichiometric reaction of prpargylic ethers: the addition now follows an anti pathway. We have

reinvestigated with these authors and compared reactivity of the various species: $RMgX + \varepsilon$ Cu(I), RCu + salt, R_2CuMgX, R_2CuLi (11). It comes out that the catalytic way gives the same result as the addition of RCu, in so far as ether is used as solvent:

(RM = $RMgX + 3\%$ Cu^I: yield 70%
= RCu : 45%)

"branched-anti" product
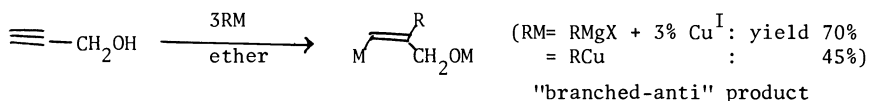
This scheme represents a rare example where anti-addition of an alkylcopper reagent occurs. When the solvent is changed to THF, however, great discrepancies are observed and the RCu reagent gives mainly the "branched-syn" adduct.
In some other cases, addition of homo- and hetero-cuprate reagents is possible with function-nalized propargylic substrates: for example, propiolic acetal reacts with magnesium homo-cuprates in THF to give a mixture of regio isomers(12), but, we have observed that the corres-ponding lithium homo- or hetero-cuprates give a regiospecific addition. Moreover, this react-ion can be extended to homologous disubstituted acetals(13):

$$Me-C\equiv C-CH(OMe)_2 \xrightarrow[\text{2) MeI}]{\text{1) BuCu(O-t-Bu)Li}} \quad \text{(structure)} \quad 87\%$$
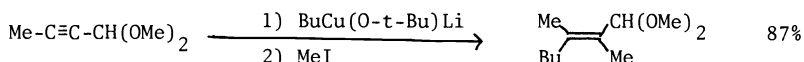
Hence a way to tetrasubstituted ethylenes.
With heterosubstituted acetylenes, a total regiospecificity can be obtained according to the hetero atom bonded to the C_{sp} atom: the addition occurs in a way corresponding to the initial polarities of the substrates.
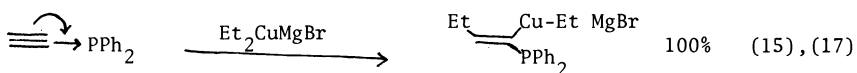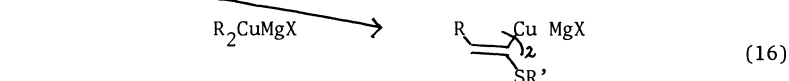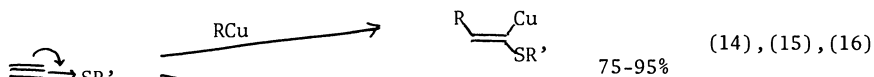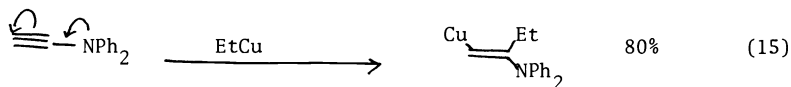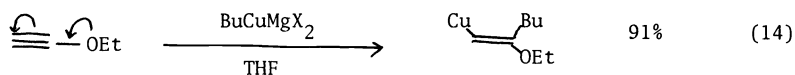
Vermeer et al. have shown that when a magnesium homocuprate is used, both alkyl moieties are transferred to the ethynyl thioether, but only one to the ethynyl phosphine. The Cu(I) catal-yzed addition of RMgX has been employed with success by the same authors only in the case of sulfurated substrates: $\equiv$-ZR (Z=S, SO, SO$_2$), but, a good stereoselectivity requires use of an excess of copper salts.
It is also possible to add an organocopper or magnesium homocuprate reagent to butadiene, in so far as secondary or tertiary substrates are concerned. The allylic copper compound thus formed reacts with electrophiles by poles 1 or 3 (18):
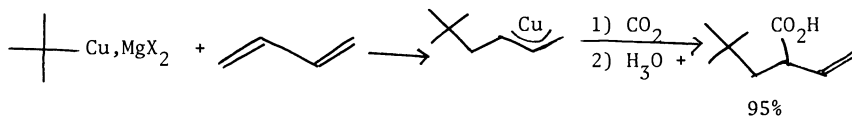
More recently, we have studied the case of conjugated enynes(19): Magnesium homocuprates add to vinyl acetylene stereoselectively on the C$\equiv$C triple bond, whereas RCu reagents or Cu(I) catalyzed reactions of Grignards give low yields. These reactions, independently described by Vermeer et al.(20), provide a new way to dienes, since saturated Grignards or organolithium compounds add to the C=C double bond, or in a 1-4 way across the enyne.
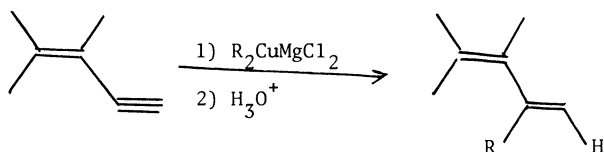
II ALKYLATION BY SUBSTITUTION REACTIONS

A-Stoichiometry

The alkylation of organic halides or pseudo halides by nucleophilic derivatives of copper has been one of the most attractive feature of these compounds. Saturated or vinyl copper reagents are much less reactive than their "ate" complexes. However, in the presence of HMPT and triethylphosphite, we have shown that alkyl halides react with the former reagents(5):


[RX=MeI: 63%; n-Bu: 58%; EtOCH$_2$Br: 85%]
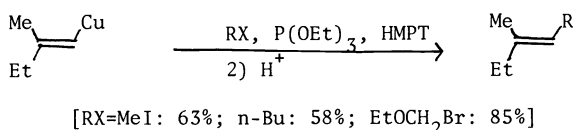
1-Bromo- or 1-iodo-1-alkynes also react with vinyl copper reagents, but, tetramethylethylene-diamie(TMEDA) has to be added, to prevent tne concurrent formation of the symmetrical diyne and diene. The corresponding enynes are thus easily obtained, particularly the cis ones of difficult access(21).



[R'= Bu: 77%; R'= SiMe$_3$" 82%; R'=CH$_2$OTHP: 82%]
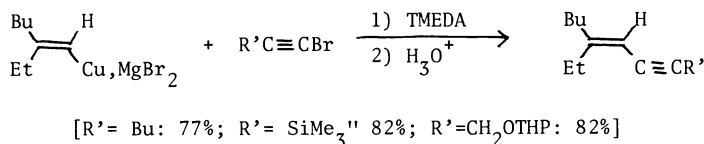
B-Catalysis

1) Vinylic substrate

Alkylation of various electrophiles (RX, ROTs,) by Grignards is subject to transition metal catalysis. As far as copper is concerned, we have shown that alkylation of vinyl iodides is easily performed under catalytic conditions, and gives better yields than the stoichiometric use of lithium dialkylcuprates. RCu compounds are much less efficient, and in a general way, copper catalyzed reactions can be carried out at room temperatures above the decomposition threshold of the corresponding organocopper reagent. For example, while stable organocopper reagents substitute vinyl iodides in pyridine:

R=Ph   99%

R=BuC≡C 85%
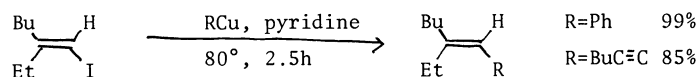
Most alkyl copper compounds fail to react. On the contrary, the catalytic mode allows alkylation by primary as well as secondary and tertiary Grignard reagents(22):

R= n-Bu   70%

i-Pr   70%

t-Bu   70%
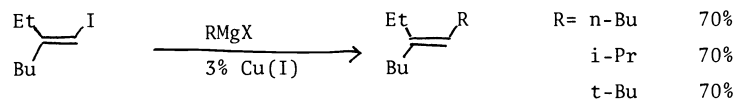
The mechanism of this reaction has been studied, taking into account the nature of the two by products:

70%   5%   25%
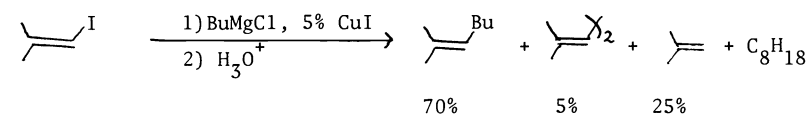
A diene, the formation of which is favoured when copper metal is present(i.e. at too high a temperature); but also an alkene, originating from a metal-halogen exchange, which has been

established by carbonation of the intermediate vinyl Grignard. We think that the reactive intermediate is a homocuprate reagent (at -20°, RCuX,MgX is not reactive towards vinyl iodides) and that the role of THF, contrary to ether, is to promote its formation. This "ate" complex gives an oxidative addition with two possible outcomes (route 1 or 2). If we assume that, in the presence of an excess of Grignard, the unsymmetrical alkyl-vinyl "ate" complex is in equilibrium with the vinyl Grignard and RCu, we can propose the following catalytic cycle:
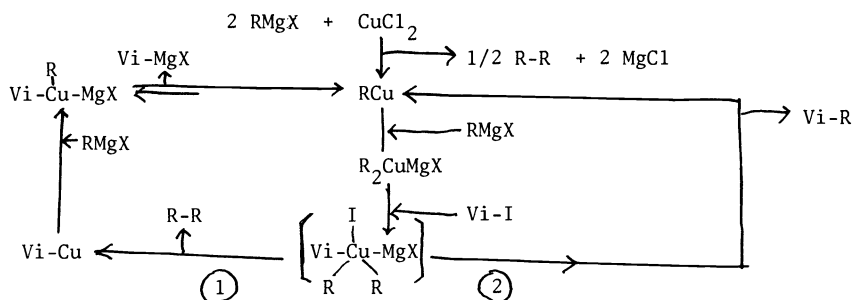

2) Saturated alkyl substrates

In the aliphatic saturated series, the Kochi's catalyst $CuCl_4Li_2$ is now well known(23), and commonly used for the condensation of Grignards with alkyl halides, or tosylates. Friedman (24) has shown that α,ω-dihaloalkanes are substituted once only by Grignards in the presence of this catalyst, but the reaction fails with α,β-dihaloalkanes, as β-elimination is the only observed reaction, as was the case with homocuprates(25).
However, the selective attack of 1,2-bis heterosubstituted alkanes would be a useful scheme in synthesis. Johnson and Dutra have shown that glycol bromohydrin tosylate is selectively substituted in ether by lithio-homocuprates in excess(26):
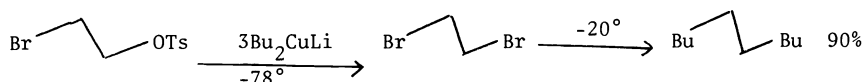

We have reinvestigated this type of reaction under the catalytical aspect(27), and only bisubstitution is observed, but elimination is no more themajor pathway.
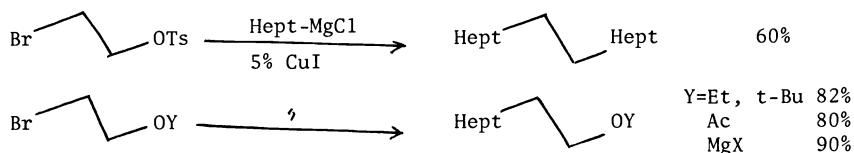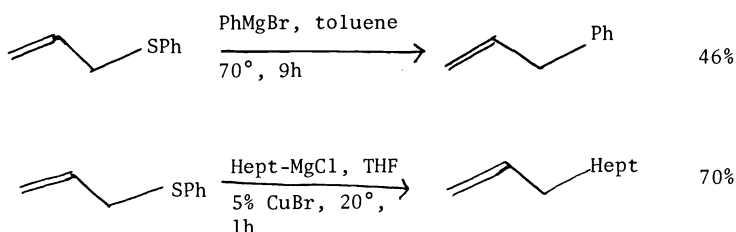

If we turn to bromoethers, a clean substitution takes place at -15°, whereas without catalysis, Grignard had shown that only elimination occurred. Stoichiometric cuprates also give this type of substitution, but need an excess of the organometallics(28),(29). Moreover, the alcohol can be free or even blocked by an acetate group, substitution is still much more rapid than elimination or addition to the carboxyl moiety(30).

3) Allylic substrates

The substitution of heteroatomic leaving groups in allylic position has been obtained with lithium homocuprates(31). Grignards in the presence of small amounts of Cu(I) can displace allylic acetates(32) and dienyl acetates(21) with conservation of the double bond geometry. We have studied the case of various other leaving groups, and generally good yields of substitution are obtained. for example, allyl phosphates react much faster in the presence of a Cu(I) catalyst(33):

[R= n-Bu, i-Pr, t-Bu, vinyl, ethynyl. yields 80-92%]
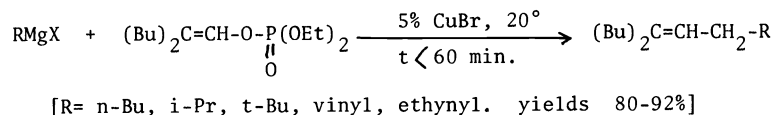
Allyl phenyl sulfides had been reacted with Grignards in a slow reaction which now occurs rapidly at room temperature(35):

$$\text{(allyl-SPh)} \xrightarrow[\text{70°, 9h}]{\text{PhMgBr, toluene}} \text{(allyl-Ph)} \quad 46\%$$

$$\text{(allyl-SPh)} \xrightarrow[\substack{\text{5\% CuBr, 20°,} \\ \text{1h}}]{\text{Hept-MgCl, THF}} \text{(allyl-Hept)} \quad 70\%$$

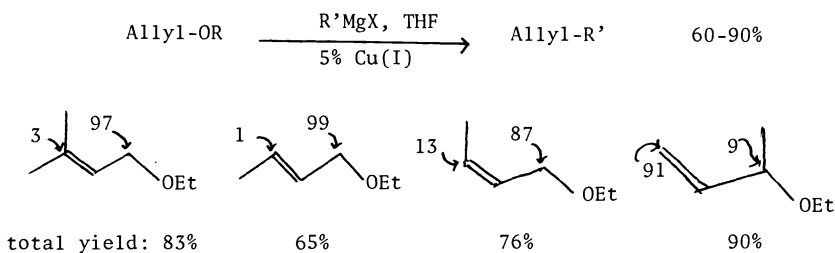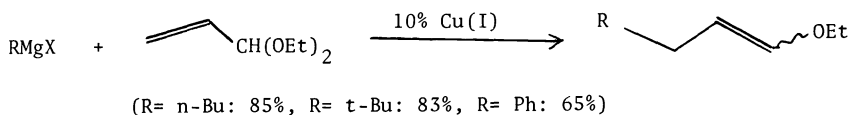In the case of allyl sulfonium halides, catalysis by Cu(I) salts proves to be very effective; not only higher yields are obtained, but the SN_2/SN'_2 ratio is increased, and a variety of Grignards can be used:
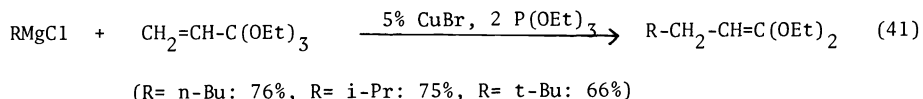

	Y%	1	2
Hept-MgCl (24h, 25°)	44	30	70
Hept-MgCl + 5% CuBr (1h, 0°)	85	80	20
tert-AmylMgCl + 5% CuBr	75	95	5
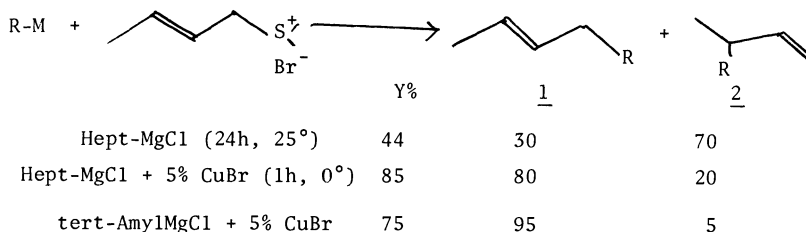
The case of allyl ethers had been studied by Kharasch et al.(36), who used conditions where no condensation occur$S$, but instead a reduction to the alkene. More recently, Claesson et al.(37) showed that nucleophilic substitution of allylic glycol monoethers was possible but obtained low yields with simple ethers. We have shown that the most important point is the use of the polar THF, as sole solvent: under this condition, a clean substitution occurs at +10, +20°, and we have studied the influence of substituents on the SN_2/SN'_2 ratio: primary ethers are mainly substituted on the functionnalized carbon atom(38):

$$\text{Allyl-OR} \xrightarrow[\text{5\% Cu(I)}]{\text{R'MgX, THF}} \text{Allyl-R'} \quad 60\text{-}90\%$$

total yield: 83%	65%	76%	90%

This reaction has been further extended to the case of α-ethylenic acetals(39), which had been formerly reacted with Grignards without a catalyst at high temperature(40) to give mixtures of allyl- and vinyl ethers. In the presence of THF and Cu(I), a clean reaction occurs below 0°, with complete rearrangement, leading to the enol ether of the aldehyde. This scheme represents a rapid way from RX to the aldehyde with three more carbon atoms.

$$\text{RMgX} + \text{(CH}_2\text{=CH-CH}_2\text{-CH(OEt)}_2) \xrightarrow{\text{10\% Cu(I)}} \text{R}\diagdown\diagup\diagdown\diagup\diagdown\text{OEt}$$

(R= n-Bu: 85%, R= t-Bu: 83%, R= Ph: 65%)

The same scheme holds for vinylic orthoesters which are converted to ketene acetals:

$$\text{RMgCl} + \text{CH}_2\text{=CH-C(OEt)}_3 \xrightarrow{\text{5\% CuBr, 2 P(OEt)}_3} \text{R-CH}_2\text{-CH=C(OEt)}_2 \quad (41)$$

(R= n-Bu: 76%, R= i-Pr: 75%, R= t-Bu: 66%)

In conclusion, the formation of alkenes with a given geometry, has been obtained via addition of organo-copper or organocuprate reagents to acetylenic substrates. Regio- and stereo-selectivity depend on the nature of the solvent, of the lithium or magnesium salts present in the solution, and of extrafunctionnalities born by the substrate. Some disubstituted alkynes also react in the same way. The organovinylcopper reagents thus formed can be

trapped with various electrophiles, particularly carbon dioxide.

As for nucleophilic substitution, use of Grignards with a catalytic amount of copper (I) salts often proves to be more rewarding than the use of stoichiometric reagents: this holds true particularly in respect of allylic hetero substituted substrates.

All these new possibilities show a common feature: the mildness of reaction condition and the selectivity of attack. However, new efforts are needed to determine precisely the exact nature of the intermediates involved in the stoichiometric as in the catalytic process, and also the influence of solvents and salts.

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