ORGANOCOPPER REAGENTS FOR THE SYNTHESIS OF SATURATED, AND 
α,β-ETHYLENIC ALDEHYDES AND KETONES

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Abstract - Conjugate addition of organocopper reagents to α,β-ethyl- 
enic aldehydes is discussed. Use of α,β-ethylenic aminals is an— 
other approach to the same target, namely homologation of R-M to an 
aldehyde with three more carbon atoms. The α,β-ethylenic aldehydes 
are easily prepared by carbocupration of α,β-acetylenic acetals. A 
new way to α,β-ethylenic ketones, mediated by organo copper reagents 
is disclosed.

INTRODUCTION

The conjugate addition of organo copper reagents to α,β-unsaturated ketones 
and esters is used commonly in organic synthesis. Several mechanisms have 
been put forward to rationalise the influence of the substrate (degree of 
substitution) and the influence of solvents or ligands. The most useful 
approach has been disclosed by House, who correlates the feasibility of such 
a reaction, with the ability of the substrate to accommodate a single electron 
in the antibonding $\pi*$ system of the ethylenic substrate: the higher the 
reduction potential (always negative vs s.c.e.) the more stable the radical 
anion. An empirical rule, using increments, allows prediction for the 
reduction potential of enones

$$
\text{R}^\text{R'} \text{C-R}^\text{R''} \xrightarrow{e} \text{R}^\text{R'} \text{C-R}^\text{R''} \text{R}
$$

R=H : -1.9 volts 1 volt = 23.05 kcal/mole

Alkyl groups (donors) are destabilizing by -0.1 V., alkoxy groups also, if 
located at R,R'R or R''(-0.3 V) whereas a phenyl group stabilizes the radical 
anion by + 0.4 V. when at R or R'R or R'' position.

The real intermediacy of a radical anion has, however, been questioned and 
some elegant experiments have focussed on the related intermediacy of a 
copper III species, which could be, in turn, viewed in a more plausible way 
as a copper II reagent where two copper atoms of the cuprate dimer release 
electron each.

The counter ion (lithium in most cases) is also considered as important 
since its coordination to the oxygen of the enone is a necessary first step.

The solvent also plays a role: addition of excess 12-crown-4-polyether 
inhibits the addition, and good donor solvents (THF, DME, DMF) retard 
conjugate addition whereas best results are observed in Et$_2$O-Me$_2$S or 
Et$_2$O-pentane mixtures.

The conjugate addition of cuprates to α,β-unsaturated aldehydes, on the 
contrary, had not been systematically studied, since contradictory reports 
had shown that only 1-2 addition was operating. Here too, in fact, the 
various parameters discussed above have to be considered: scattered examples 
of the conjugate addition were described when we undertook a systematic 
survey of this reaction. Lithium dimethyl cuprate adds to various enals, 
with erratic yields when the reaction is quenched by an acidic or an 
ammonium chloride solution, since aldolisation-crotonisation products are 
formed. On the contrary, trapping of the enolate species by trimethyl silyl
chloride leads to reproducible yields (see table 1)

\[ \text{Bu}_2\text{CuLi} + \text{CHO} \rightarrow \text{Bu} \equiv \text{CHOSiMe}_3 \]

Acrylon and \( \alpha - \) or \( \beta - \) monosubstituted acroleins give practically only products originating from conjugate addition (see table 1); \( \alpha,\beta - \) or \( \beta,\beta - \) disubstituted olefins give a small amount of 1-2 attack, which becomes more important with \( \alpha,\beta,\beta - \) trisubstituted acroleins. In the latter case, an improvement has been disclosed by Clive et al.\(^{12}\), by using the higher order cuprate \( \text{Me}_5\text{Cu}_3\text{Li}_2 \) instead of \( \text{Me}_2\text{CuLi} \).

Table 1 - Addition of lithium dimethyl cuprate to various enals, ratios of conjugate-versus carbonyl addition (Ether solvent)

<table>
<thead>
<tr>
<th>Yield %</th>
<th>1-4/1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-CHO</td>
<td>77</td>
</tr>
<tr>
<td>CHO</td>
<td>74</td>
</tr>
<tr>
<td>CHO</td>
<td>85</td>
</tr>
<tr>
<td>CHO</td>
<td>86</td>
</tr>
<tr>
<td>CHO</td>
<td>85</td>
</tr>
<tr>
<td>CHO</td>
<td>86</td>
</tr>
<tr>
<td>Me\text{\textsubscript{5}Cu\textsubscript{3}Li\textsubscript{2}}</td>
<td>86</td>
</tr>
</tbody>
</table>

The solvent plays an important role: the less polar ones being the more favorable:

<table>
<thead>
<tr>
<th>Yield %</th>
<th>1-4/1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{EtMeCuLi} + \text{CHO}</td>
<td>75</td>
</tr>
<tr>
<td>Ether pentane</td>
<td>85</td>
</tr>
<tr>
<td>Ether</td>
<td>85</td>
</tr>
<tr>
<td>THF</td>
<td>55</td>
</tr>
</tbody>
</table>

and a low temperature (-50\(^{\circ}\) instead of 0\(^{\circ}\)C) also improves the 1-4/1-2 ratio.

A generalization of these results to a variety of cuprates has been performed (see table 2). It turns out that allylic cuprates only give 1-2 addition as they do with \( \alpha,\beta - \) enones. Secondary cuprates give a 1/1 ratio of 1-4 versus 1-2 addition: it is known\(^{7}\) that ditertiobutyl cuprate has a tendency to add partly in such a way to enones; \( \alpha - \) branching of the cuprates thus impedes conjugate addition. On the contrary, phenyl, vinyl and homoallyl cuprates give exclusively the 1-4 addition.
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Table 2 - Addition of various lithium cuprates to α,β-enals in ether

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Temperature</th>
<th>Yield %</th>
<th>1-4/1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuLi + CHO</td>
<td>-45°</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>CuLi + CHO</td>
<td>-70°</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>CuLi + CHO</td>
<td>-45°</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>CuLi + CHO</td>
<td>-45°</td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>CuLi + CHO</td>
<td>-30°</td>
<td>66</td>
<td>100</td>
</tr>
</tbody>
</table>

Other organocopper reagents may also be used: Methyl copper derived from the Grignard reagent or the lithium reagent gives a high ratio of 1-4 addition.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Temperature</th>
<th>Yield %</th>
<th>1-4/1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCuLi + CHO</td>
<td>0° 8h</td>
<td>65</td>
<td>93/7</td>
</tr>
<tr>
<td>MeCu MgBr2 +</td>
<td>0° 3h</td>
<td>68</td>
<td>94/6</td>
</tr>
<tr>
<td>Me2Cu + CHO</td>
<td>-50° 1h</td>
<td>85</td>
<td>82/18</td>
</tr>
<tr>
<td>Me2Cu MgBr +</td>
<td>0° 1h</td>
<td>50</td>
<td>99/1</td>
</tr>
</tbody>
</table>

but in the case of cuprate reagents, the magnesium cuprate, although less reactive than its lithium counterpart, gives an almost regioselective 1-4 addition. We found that the magnesium cuprates were very efficient if prepared from the CuBr,Me2S complex. This complex has proved useful in many reactions of cuprates, but never such a dramatic influence of CuBr,Me2S versus CuBr has been described so far to our knowledge. The polarity of the solvent, which was a determining factor in the case of lithio cuprates, is now of minor importance.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Yield %</th>
<th>1-4/1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu2CuMgCl + Me3SiCl</td>
<td>from CuBr THF (ether)</td>
<td>73-27</td>
</tr>
<tr>
<td></td>
<td>from CuBr,Me2S THF</td>
<td>96-4</td>
</tr>
</tbody>
</table>

Under these conditions, secondary magnesium cuprates give an exclusive 1-4 addition:

\[(iPr)_2CuMgClMe_2S + n.PrCHO \rightarrow n.PrCH-CH_2CHO\]

72%

Lastly, magnesium cuprates are the best reagents for the conjugate addition to acrolein:

\[Bu_2CuMgCl, Me_2S + Me_3SiCl + CHO \rightarrow OSiMe_3\]

84%

(60% only from the corresponding lithio cuprate)

The case of α-halo α-ethylenic aldehydes also shows that these substrates are prone to undergo conjugate addition. One can "a priori" anticipate four distinct pathways:

\[\text{CHO} + R_2CuLi\]

"1,4" reduction M/X exchange

"1-2"
When X is chlorine, only 1-4 addition is observed:

\[ \text{n.Pr-CH=CCl-CHO} \xrightarrow{1/ \text{Me}_2\text{CuLi}} \text{n.Pr-CH-CH-CHO} \xrightarrow{2/ \text{H}_2\text{O}} \text{Me Cl} \]

\[
\text{Cl} \quad \text{CHO} \\
\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
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Thus, starting from the commercially available (+) or (-) ephedrin, it is possible to prepare the corresponding oxazolidine which is obtained as an almost pure (95%) diastereoisomer.

Addition of a lithium dialkyl cuprate, followed by hydrolysis over acidic silica, yields an aldehyde with ee of about 40%.

Interconversion of the R and R' groups in the substrate and the reagent results in the opposite configuration as does the change from (+) to (-) ephedrin in the starting oxazolidine.

This approach has been successfully used for a synthesis of (+) citronellal according to:

but suffers from several limitations:
- α-substituted α,β-ethylenic aldehydes do not give oxazolidines with ephedrin
- β,β-disubstituted-α,β-ethylenic aldehydes may undergo isomerisation of the C=C double bond during the oxazolidine formation.

ACCESS TO α,β-ETHYLENIC ALDEHYDES AND KETONES

The last part of my talk is devoted to the preparation of α,β-ethylenic aldehydes or ketones, in order to show that organocopper reagents are valuable partners for the synthesis of such compounds.

We have found that the carbometallation of propynal acetal can be performed regioselectively, according to the nature of the organocopper species: a lithium dialkyl cuprate in ether leads to the linear "L" isomer whereas a magnesium dialkyl cuprate in THF yields the isomeric branched reagent ("B")
Thus a large variety of α-ethylenic acetals may be prepared, and even the methyl cuprate, known to give a very sluggish addition to terminal alkynes, reacts more easily in this case:

\[
\text{MeCuSPhLi} + \text{Me} \equiv \text{CH(OMe)}_2 \xrightarrow{\text{Cuprate}} \text{Me} \equiv \text{CH(OMe)}_2 + \text{LiCu}_2(\text{OMe})_2
\]

The corresponding vinylic cuprates can be trapped with a variety of electrophiles:

\[
\text{Et}_2\text{CuLi} + \text{Me} \equiv \text{CH(OEt)}_2 \xrightarrow{1/\text{Et}_2\text{CuLi}} \text{Et} \equiv \text{CH(OEt)}_2 \quad (85\%)
\]

Even the poorly reactive 1-iodo-1-alkenes have been condensed in the presence of a Pd° catalyst under a cascade of transmetallations:

\[
\text{Et}_2\text{CuLi} + \text{Me} \equiv \text{CH(OMe)}_2 \xrightarrow{1/\text{Et}_2\text{CuLi}} \text{Me} \equiv \text{CH(OMe)}_2 \xrightarrow{5/\text{Bu}_{\text{A}}\_\text{I}} \text{Bu} \equiv \text{CH(OMe)}_2 \quad (72\%)
\]

which is interpreted by the following scheme:

\[
\text{V}i_2\text{CuLi} \xrightarrow{\text{MgX}_2} \text{V}i_2\text{CuMgX} \xrightarrow{\text{ZnX}_2} \text{V}i\text{Cu,MgX}_2 + \text{V}i\text{ZnX}
\]

the vinyl zinc reagent, as well as the vinyl copper-magnesium salt reagents being able to react with the catalytically formed hexenyl palladium iodide.

The acetals thus formed can be deprotected to the corresponding aldehydes with retention of configuration of the ethylenic linkage (particularly with acetic acid-water-dichloromethane mixtures).

An other approach to α,β-ethylenic ketones (but not aldehydes) has been studied more recently: viz the coupling of an acid halide with a vinyl copper reagent. The reaction, which is well known for the alkyl copper analogues, may be thwarted here by an immediate addition of the starting cuprate to the newly formed enone:

\[
\text{RCOCl} + \text{Me} \equiv \text{CO-R} \xrightarrow{\text{Et}_2\text{CuLi}} \text{Et} \equiv \text{CO-R}
\]
Indeed vinyl copper reagents (from Grignards) give rather poor yields of acylated products, and better yields could be attained from lithium cuprate in the presence of HMPT.

\[
\begin{align*}
&\text{RCuMgX}_2 + R'C=CH \rightarrow R'C\equiv\text{CuMgX}_2 \\
&\text{RCuMgX}_2 + R''\text{COCl} \rightarrow R''\equiv\text{CuMgX}_2 \\
&\text{Hept}_2\text{CuLi} + \text{HC}=\text{CH} \rightarrow \text{Hept}_2\text{CuLi} + \text{BuCOCl} + 2\text{MgCl}_2 + \text{CuBr} \\
&\text{Hept}_2\text{CuLi} + \text{BuCOCl} + 2\text{MgCl}_2 + \text{CuBr} \rightarrow \text{Hept} + \text{Me} \quad (60\% \text{ from CH}_3\text{COBr})
\end{align*}
\]

We have now found that reagents A or B can be acylated with good yields and excellent isomeric purity if a Pd° catalyst is present:

\[
\begin{align*}
&\text{R}^+\equiv\text{Cu,MgX}_2 + \text{R}''\text{COX,THF} \rightarrow \text{R}''\equiv\text{Cu,MgX}_2 \\
&\text{Bu}_2\text{CuLi} + \text{BuCOCl} + 2\text{MgCl}_2 + \text{CuBr} + 3\% \text{Pd}^\circ \text{L}_4 \\
&\text{Bu}_2\text{CuLi} + \text{BuCOCl} + 2\text{MgCl}_2 + \text{CuBr} + 3\% \text{Pd}^\circ \text{L}_4
\end{align*}
\]

Under these conditions, even mixed carbonic-carboxylic anhydrides may be used:

\[
\begin{align*}
&\text{MeCu,MgX}_2 + \text{EtCOCl} + 3\% \text{Pd}^\circ \text{L}_4 \\
&\text{MeCu,MgX}_2 + \text{PhCOCl} + 3\% \text{Pd}^\circ \text{L}_4 \\
&\text{MeCu,MgX}_2 + \text{MeCOCl} + 3\% \text{Pd}^\circ \text{L}_4
\end{align*}
\]

and \(\alpha,\alpha'^\prime\)-diethylenic ketones with a given geometry for both C=C double bonds are accessible:

In conclusion the conjugate addition of organocopper reagents to \(\alpha,\beta\)-ethylenic aldehydes is a general way of homologation to a saturated aldehyde with three more carbon atoms. \(\alpha\)-Ethylenic chiral aminals may also be used for such a strategy if a chiral \(\beta\)-substituted aldehyde is the target of the synthesis. The starting ethylenic aldehydes are easily prepared by carbocupration of \(\alpha\)-acetylenic acetalts, and even \(\alpha\)-ethylenic ketones can be prepared via palladium catalysed acylations of organo copper reagents.

ACKNOWLEDGEMENTS

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20. With chiral organometallics:
With chiral substrate:
For an analogous study see also:
29. Better yields have been obtained in some cases, see: