

## ORGANOCOPPER REAGENTS FOR THE SYNTHESIS OF SATURATED, AND $\alpha,\beta$ -ETHYLENIC ALDEHYDES AND KETONES

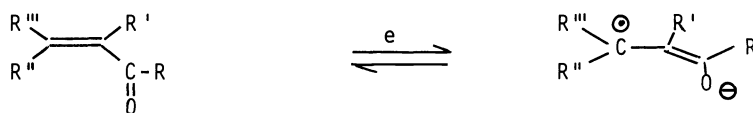
A. Alexakis, C. Chuit, M. Commerçon-Bourgain, J.P. Foulon, N. Jabri,  
P. Mangeney, J.F. Normant

Laboratoire de Chimie des Organoéléments, Université P. & M. Curie  
4 place Jussieu 75230 PARIS Cédex 05 - France

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

### INTRODUCTION

The conjugate addition of organo copper reagents to  $\alpha,\beta$ -unsaturated ketones and esters is used commonly in organic synthesis<sup>1</sup>. 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<sup>2</sup>: 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



R=H : -1.9 volts

1 volt  $\equiv$  23.05 kcal/mole

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

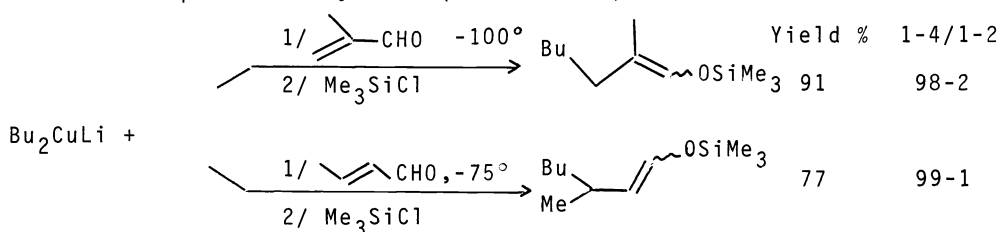
The real intermediacy of a radical anion has, however, been questioned and several elegant experiments have focussed on the related intermediacy of a copper III species, which could be, in turn, viewed in a more plausible way as a copper II reagent where two copper atoms of the cuprate dimer release one electron each<sup>4</sup>.

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<sup>5</sup>.

The solvent also plays a role: addition of excess 12-crown-4-polyether inhibits the addition<sup>6</sup>, and good donor solvents (THF, DME, DMF) retard conjugate addition whereas best results are observed in Et<sub>2</sub>O-Me<sub>2</sub>S or Et<sub>2</sub>O-pentane mixtures<sup>7</sup>.

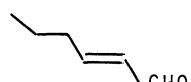
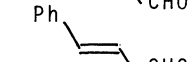
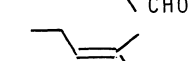
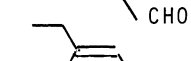

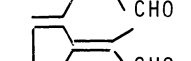

The conjugate addition of cuprates to  $\alpha,\beta$ -unsaturated aldehydes, on the contrary, had not been systematically studied, since contradictory reports had shown that only 1-2 addition was operating<sup>8-9</sup>. Here too, in fact, the various parameters discussed above have to be considered: scattered examples of the conjugate addition were described<sup>10</sup> when we undertook a systematic survey of this reaction<sup>11</sup>. 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)



Acrolein 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.*<sup>12</sup>, 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)

	Yield %	1-4/1-2
	77	99/1
	74	"
	85	92/8
	86	95/5
	85	81/19
	86	36/64
	86	78/22 <sup>12</sup>

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

	Yield %	1-4/1-2
$\text{Me}_2\text{CuLi} + \begin{array}{c} \text{Et} \quad \text{Me} \\ \text{---} \\ \text{CHO} \end{array}$	$\xrightarrow{\text{Ether pentane}}$	75 95/5
	$\xrightarrow{\text{Ether}}$	85 82/18
	$\xrightarrow{\text{THF}}$	55 40/60

and a low temperature ( $-50^\circ$  instead of  $0^\circ\text{C}$ ) 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<sup>7</sup> 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 homo-allyl cuprates give exclusively the 1-4 addition.

Table 2 - Addition of various lithium cuprates to  $\alpha,\beta$ -enals in ether

			Yield %	1-4/1-2
	+	Pr-CH=CH-CHO $\xrightarrow{-45^\circ}$	72	0 <u>100</u>
	+	CH=CH-CHO $\xrightarrow{-70^\circ}$	65	45 55
	+	CH=CH-CHO $\xrightarrow{-45^\circ}$	95	<u>100</u> 0
	+	CH=CH-CHO $\xrightarrow{-45^\circ}$	77	<u>100</u> 0
	+	CH=CH-CHO $\xrightarrow{-30^\circ}$	66	<u>100</u> 0

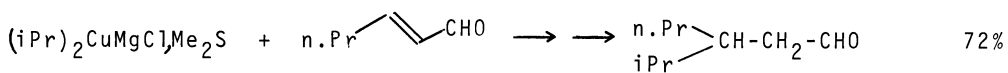
Other organocopper reagents may also be used<sup>11,13</sup>: Methyl copper derived from the Grignard reagent or the lithium reagent gives a high ratio of 1-4 addition,

			Yield %	1-4/1-2
MeCu, LiI	+	$\xrightarrow{0^\circ \text{ 8h}}$	65	93/7
MeCu MgBr <sub>2</sub>	+	" $\xrightarrow{0^\circ \text{ 3h}}$	68	94/6
Me <sub>2</sub> CuLi	+	" $\xrightarrow{-50^\circ \text{ 1h}}$	85	82/18
Me <sub>2</sub> Cu MgBr	+	" $\xrightarrow{0^\circ \text{ 1h}}$	50	99/1

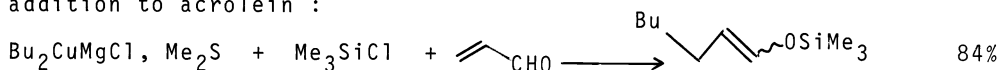
but in the case of cuprate reagents, the magnesium cuprate, although less reactive than its lithium counterpart, gives an almost regioselective 1-4 addition. We found that the magnesium cuprates were very efficient if prepared from the CuBr, Me<sub>2</sub>S complex<sup>14</sup>. This complex has proved useful in many reactions of cuprates<sup>15</sup>, but never such a dramatic influence of CuBr, Me<sub>2</sub>S 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

Bu <sub>2</sub> CuMgCl	+		$\xrightarrow{\text{Me}_3\text{SiCl}}$	1-4/1-2	Yield %
			from CuBr THF(ether)	73-27	22
			from CuBr, Me <sub>2</sub> S THF	96-4	83

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

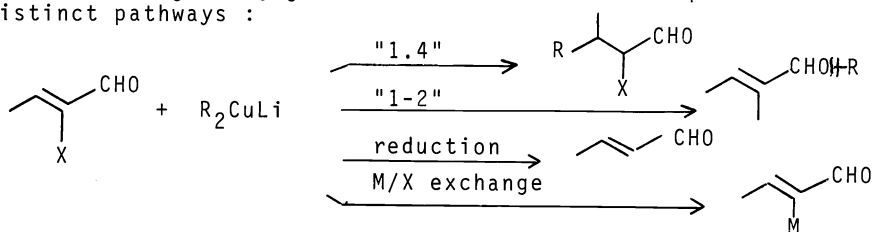


Lastly, magnesium cuprates are the best reagents for the conjugate addition to acrolein:

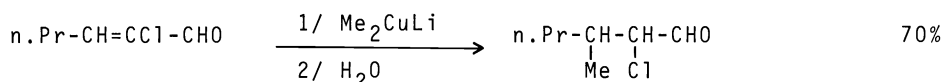


(60% only from the corresponding lithio cuprate)

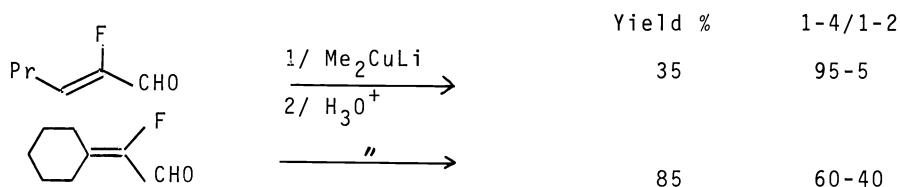
The case of  $\alpha$ -halo  $\alpha$ -ethylenic aldehydes also shows that these substrates are prone to undergo conjugate addition<sup>16</sup>. One can "a priori" anticipate four distinct pathways:



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



but the  $\alpha$ -fluoro analogs lead to mixtures :

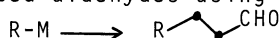


We have indeed measured that, in the case of  $\alpha$ -halo- $\alpha,\beta$ -unsaturated ketones, a chlorine atom increases the reduction potential by 0.4 V whereas a fluorine atom does so to the extent of 0.15 V. only. It is known that an enolate is less stabilized by an  $\alpha$ -fluorine atom than would be expected from inductive effects<sup>17</sup>.

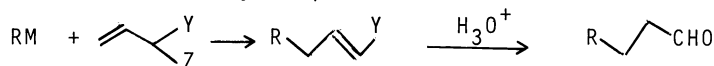
More recently<sup>18</sup>, conjugate addition of lithium dimethyl cuprate to an  $\alpha,\beta$ -ethylenic- $\alpha$ -bromo aldehyde has been shown to occur with a yield of about 40%.

#### USE OF OXAZOLIDINES

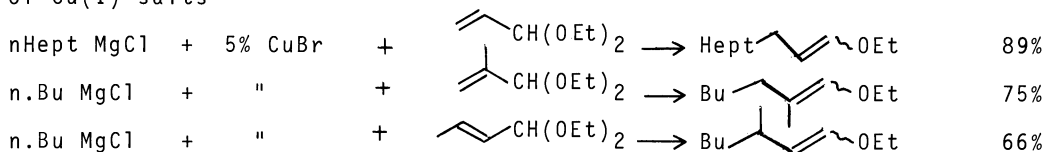
Another approach to saturated aldehydes using a 3 carbons chain extension



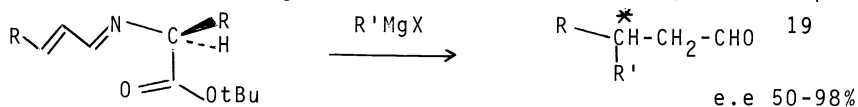
consists in the ( $\text{S}_{\text{N}}2'$  type) nucleophilic substitution of reagents bearing two geminated hetero atoms in allylic position



We had shown previously that such is the case when a Grignard reagent is reacted with an  $\alpha,\beta$  ethylenic acetal in the presence of a catalytic amount of Cu(I) salts

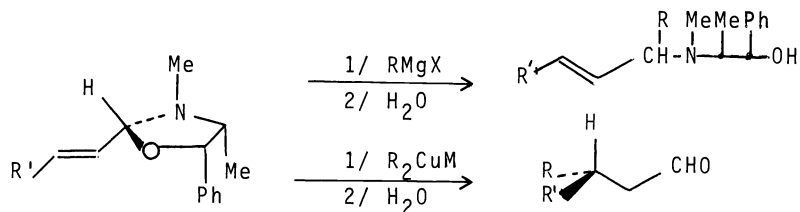


This methodology could be used for an enantioselective preparation of chiral  $\beta$ -substituted aldehydes. Such compounds have been the target of several trials using various induction schemes, for example :

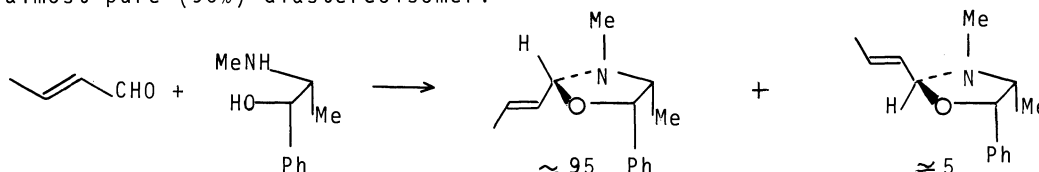


although most studies have been performed on  $\alpha,\beta$ -ethylenic ketones<sup>20</sup>, esters<sup>21</sup>, amides<sup>22</sup> or ethers<sup>23</sup>.

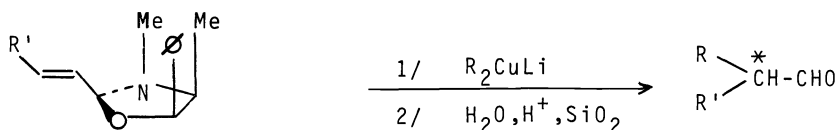
Our approach initiated from the fact that, although magnesium and lithium reagents attack allylic cyclic amino ethers on the functionalised carbon, lithium dialkylcuprates, on the other hand, attack preferentially the allylic system :



Thus, starting from the commercially available (+) or (-) ephedrin, it is possible to prepare the corresponding oxazolidinone 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%<sup>24</sup>

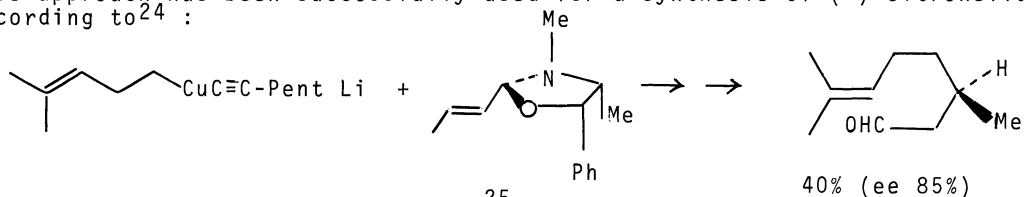


from (-) ephedrin

R	R'	ephedrin	Yield %	ee %	Config.
Me	Ph	(+)	75	51	R
Me	Ph	(-)	75	40	S
Ph	Me	(-)	45	40	R

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 oxazolidinone.

This approach has been successfully used for a synthesis of (+) citronella according to<sup>24</sup> :



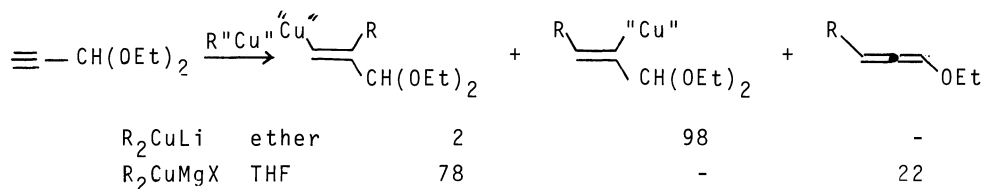
but suffers from several limitations<sup>25</sup> :

- $\alpha$ -substituted  $\alpha,\beta$ -ethylenic aldehydes do not give oxazolidines with ephedrin
- $\beta,\beta$ -disubstituted- $\alpha,\beta$ -ethylenic aldehydes may undergo isomerisation of the C=C double bond during the oxazolidine formation.

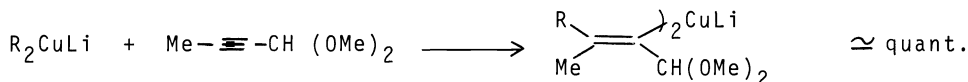
#### ACCESS TO $\alpha,\beta$ -ETHYLENIC ALDEHYDES AND KETONES

The last part of my talk is devoted to the preparation of  $\alpha,\beta$  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<sup>26</sup> : a lithium dialkyl cuprate in ether leads to the linear "L" isomer whereas a magnesium dialkylcuprate in THF yields the isomeric branched reagent ("B")

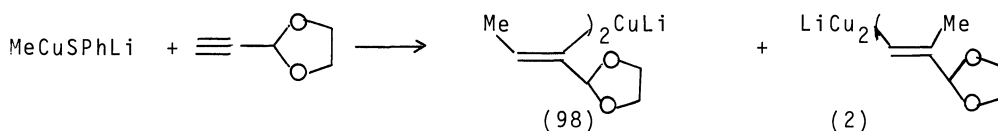


Lithium cuprates also add to disubstituted acetylenic acetals leading eventually to  $\alpha$ -ethylenic acetals with a stereospecifically tetrasubstituted ethylenic moiety

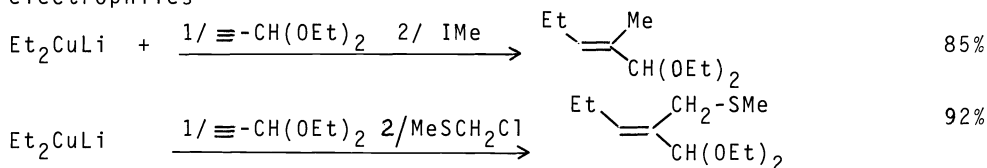


R=Et, nBu, sec Bu, ter Bu

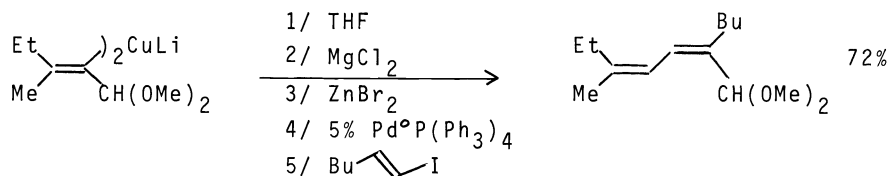
Thus a large variety of  $\alpha$ -ethylenic acetals may be prepared, and even the methyl cuprate, known to give a very sluggish addition to terminal alkynes, reacts more easily in this case :



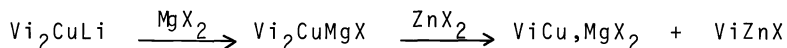
The corresponding vinylic cuprates can be trapped with a variety of electrophiles



Even the poorly reactive 1-iodo-1-alkenes have been condensed in the presence of a  $\text{Pd}^0$  catalyst under a cascade of transmetalations :



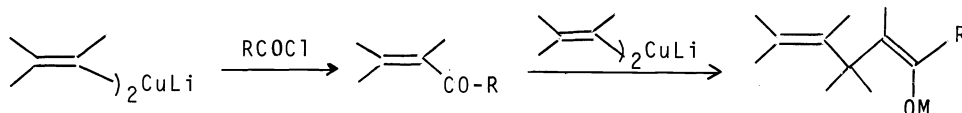
which is interpreted by the following scheme<sup>27</sup> :



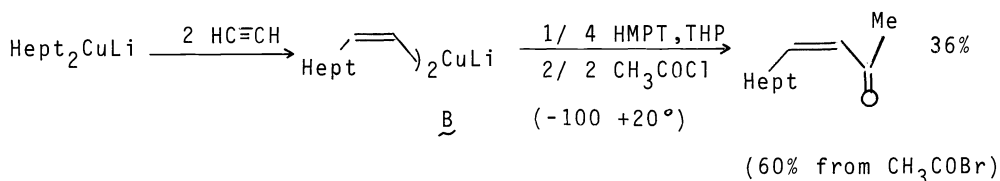
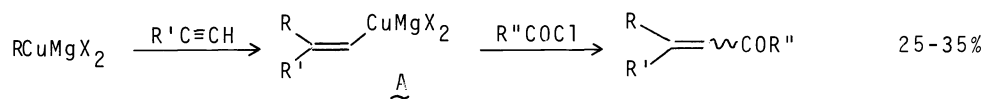
the vinyl zinc reagent, as well as the vinyl copper-magnesium salt reagents being able to react with the catalytically formed hexenyl palladium iodide.

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)<sup>26</sup>.

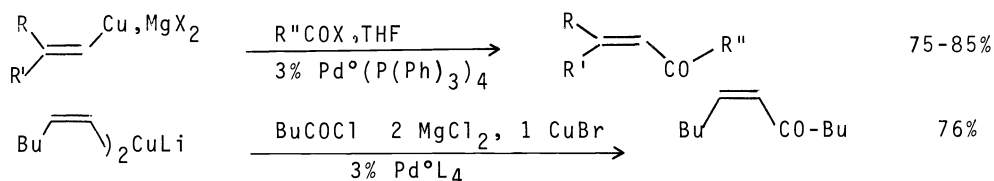
An other approach to  $\alpha, \beta$ -ethylenic ketones (but not aldehydes) has been studied more recently : viz the coupling of an acid halide with a vinyl copper reagent. The reaction, which is well known for the alkyl copper analogues<sup>28</sup>, may be thwarted here by an immediate addition of the starting cuprate to the newly formed enone :



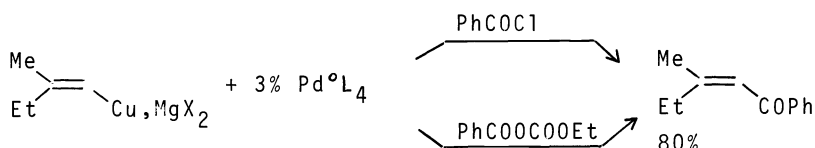
Indeed vinyl copper reagents (from Grignards) give rather poor yields of acylated products<sup>29</sup>, and better yields could be attained from lithium cuprate in the presence of HMPT<sup>30</sup>



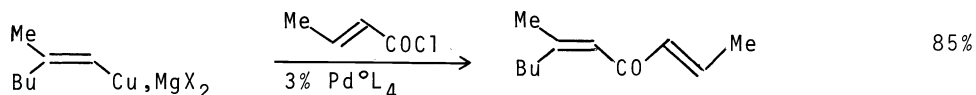
We have now found that reagents A or B can be acylated with good yields and excellent isomeric purity if a Pd<sup>0</sup> catalyst is present<sup>30</sup>:



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



and  $\alpha, \alpha'$ -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 amins 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 acetals, and even  $\alpha$ -ethylenic ketones can be prepared via palladium catalysed acylations of organo copper reagents.

#### ACKNOWLEDGEMENTS

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