New access to conjugated dienes via carbocupration of alkynes

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ORGANOCOPPER AND ORGANOMANGANOUS REAGENTS

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Part 1 PREPARATION OF CONJUGATED DIENES AND ENYNES VIA ORGANO COPPER REAGENTS

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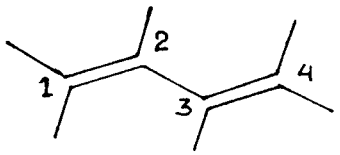
4-12 1-Ethylthio 1Z, 3E-Hexadiene

4-13 1-Ethoxy-4-Butyl-2(E), 4-pentadiene

1 - OCCURENCE and INTEREST of CONJUGATED DIENES

The conjugated diene unit is extremely widespread among natural products ; although it rapidly caught the attention of chemists and led to a detailed study of electron delocalization, cycloadditions, etc... The preparation of isomerically pure dienes, without tedious purifications, has been an important challenge for years. The goal is to prepare



mono- to hexa-substituted butadiene showing a given geometry, namely EE, E-Z, Z-E, Z-Z. Compounds of first type are generaly the most stable, and may be formed unduly during attempted synthesis of the other three types. However, they are the more useful for Diels Alder reactions, since the s-cis conformation may be adopted freely. E-Z isomers have been used however, more recently, in such 2+4 additions[1] and appear to be frequently encountered in sexual pheromones of lepidopterae. Z-Z isomers also exist in nature, but are less frequent. In the following pages, attention will be focussed on the EZ 1-4 disubstituted butadienes, and on tri, tetra ... substituted ones.

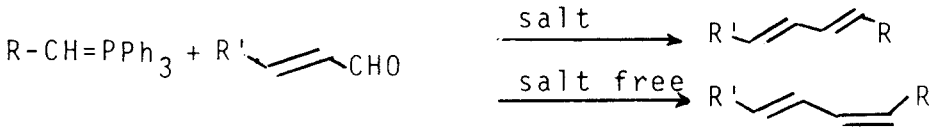
2 - VARIOUS SYNTHETIC METHODS LEADING To (mainly E,Z) DIENES

The most well known strategies to prepare these structures are the following :

2-1 Wittig Reaction

From an α,β ethylenic aldehyde (purely E if kept some time at room temperature), or Z, if prepared according to[2] with a Wittig reagent, either in the presence or

absence of lithium salts[3,4] it is theoretically possible to prepare all four types of 1-4 disubstituted 1-3 butadienes. However high purity is found only in the preparation of the E,E isomers

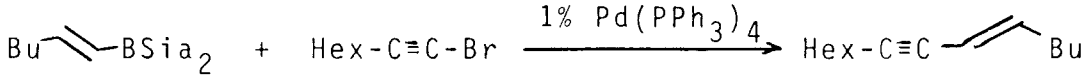


2-2 From Z-conjugated enynes

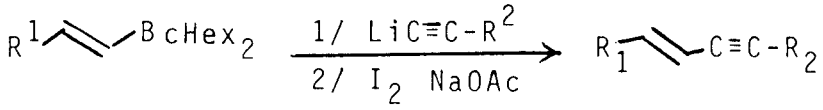
prepared from Z vinyl copper derivatives (v.i) and 1-halo-1-alkynes[5,6] or from an 1-alkyne[7] or an acetylenic Grignard[7] and a Z 1-halo-1-alkene in the presence of Pd°. A subsequent antihydrogenation of the triple bond leads to the desired Z,E diene.

2-3 From E-conjugated enynes

These may be prepared via boron chemistry, by reaction of E vinyl boranes with either 1-halo alkynes in the presence of Pd° [8,9]

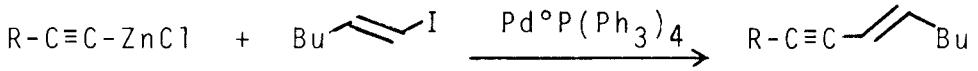


or with lithium acetylides, followed by carbon migration in the ate complex thus formed[10,11]. Use of bicyclohexyl borane

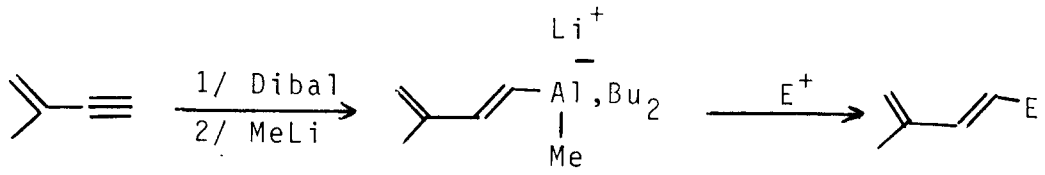


proved particularly efficient.[4]

An other excellent approach is the reaction of acetylenic Zinc chlorides with E-1-iodo-1-alkenes in the presence of Palladium[7]

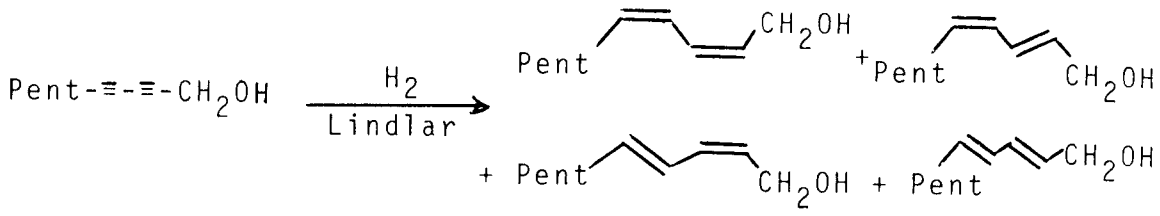


These enynes are further reduced in a Syn way by Lindlar's semi hydrogenation[13] or by bicyclohexyl[14] or disiamyl boranes[10,15] or Zinc in propanol in the presence of potassium cyanide[16]. Hydro-alanation of terminal enynes is also possible[17,18]



2-4 From diynes

It should be raised, that the Lindlar's hydrogenation of such substrates may lead to a mixture of isomers, e.g. :[19]

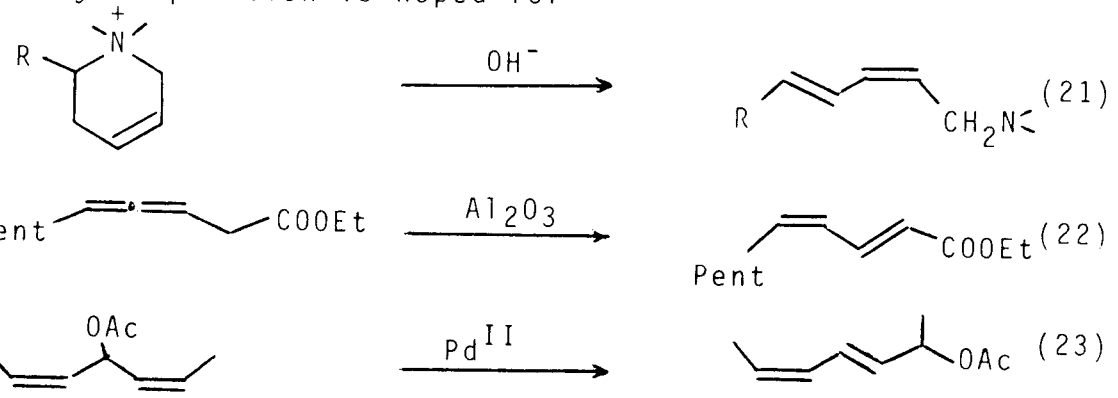


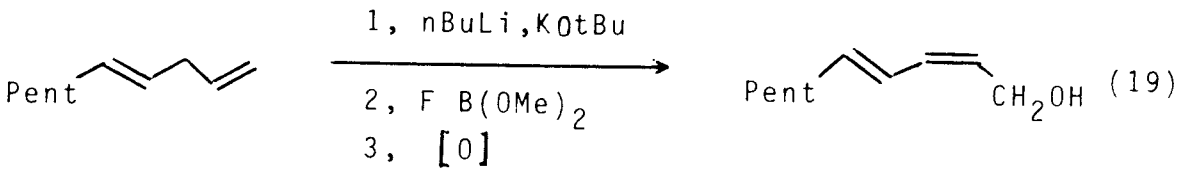
75/8/16/ 1%

but that dicyclohexyl borane has led to pure Z,Z dienes[20]

2-5 Miscellaneous methods

Specific methods can be employed when a given functionality in allylic position is hoped for



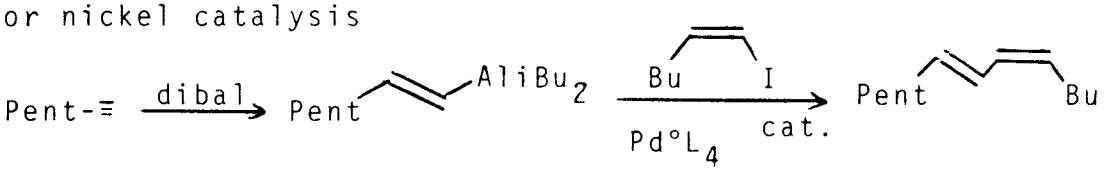


2-6 From coupling of vinyl organometallics with vinylic halides

The palladium catalyzed coupling reaction of a Z vinyl Grignard with an E-1-iodo-1 alkene gives good yields of Z-E diene, but the isomeric Z-1-iodo-1-alkene leads to a mixture of isomers.[24]

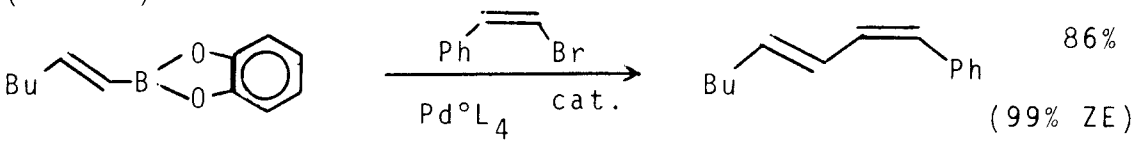
One of the most useful approach is the use of organo-vinyl Zirconium[25] or -Aluminium[26] prepared by hydrometallation of

a terminal, or internal alkyne. These reagents were shown by Negishi[27,28] to couple with 1-iodo-1 alkenes under palladium or nickel catalysis



in certain cases, it may be appropriate to switch from the alane compound, to the Zinc derivative, which couples even more efficiently[27,28]

Vinyl boranes either E or Z (the latter being less stable), also couple with E or Z 1-halo-1-alkenes, opening a way to all classes of isomeric dienes[9] under palladium catalysis (Suzuki)[8-15]

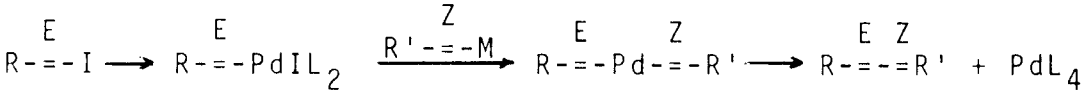


Excellent, and more detailed reviews have appeared[4,15,29,32]

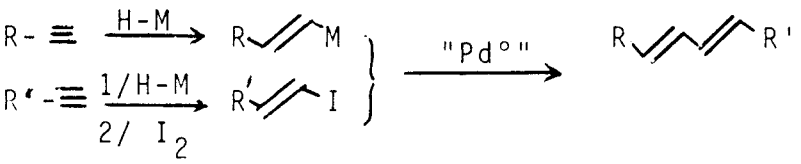
3 - USE OF ORGANO COPPER REAGENTS FOR THE SYNTHESIS OF CONJUGATED DIENES AND ENYNES

3-1 Introduction

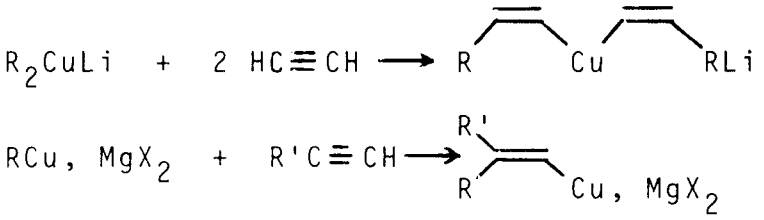
From these various examples, the last method (vinyl-vinyl coupling) is the most straight forward since retention of both vinylic partners seems to be a general pattern, through the several substitutions which occur during the palladium catalysis :



However, we are left with the problem of preparing isomerically pure reagents, and the syn hydrometallation of alkynes is best suited for the access to E units



Here is the point where organo copper chemistry may be of some help, since carbocupration of acetylenes leads, in high yields and high purity, to Z reagents, or to β,β disubstituted vinyl copper reagents of given geometry



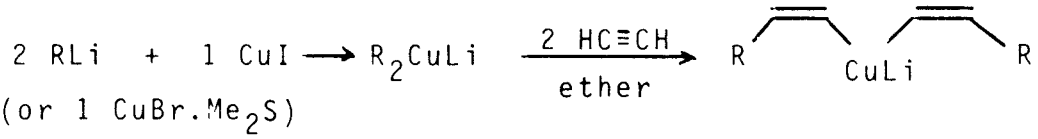
These can be iodinolyzed with total retention of configuration to the corresponding 1-iodo-1-alkenes in high yield.[33]

Also worth of note, is the fact that hydro alumination of alkynes bearing oxygenated functions is almost inoperative,[34] while hydrozirconation operates regioselectively, whatever the extra functions borne by the acetylenic substrate.[27]

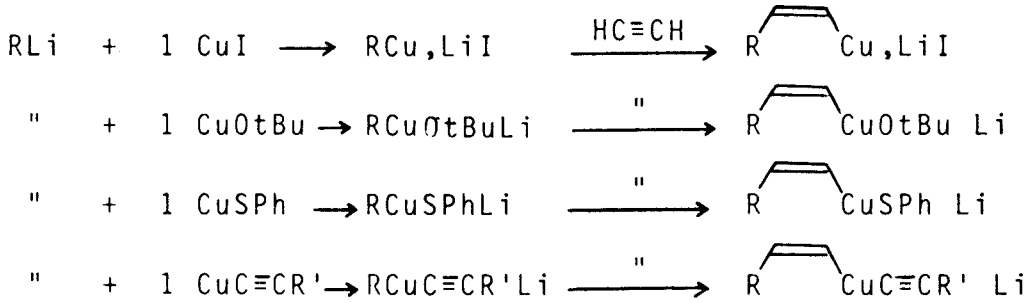
In the case of carbocupration of such functionalized alkynes, a high control of the regioselectivity may occur, according to the nature, and proximity of these functions (v.i), the nature of the solvent, and of the main group metal salts.[33]

3-2 Preparation of the vinyl copper reagents[33]

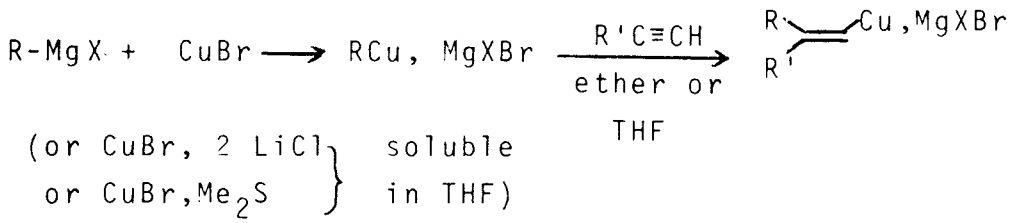
Z,β-Mono substituted vinyl copper reagents are best prepared from the corresponding lithium reagent, either converted to a homocuprate and added to two equivalents of acetylene in ether



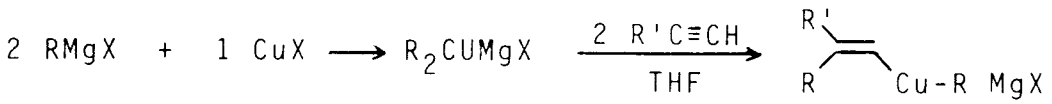
or converted to a copper reagent or to an unsymetrical cuprate and added to one equivalent of acetylene.



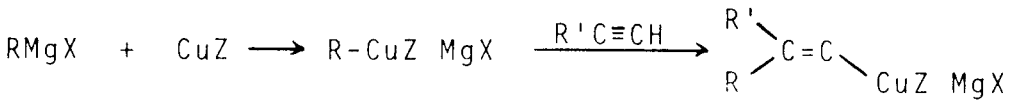
β,β disubstituted vinyl copper reagents are best prepared from the corresponding Grignard reagent, in ether or in THF



and added to a terminal alkyne. THF is best suited for secondary and tertiary alkyl copper reagents. CuBr,Me_2S in a Me_2S-ether mixture leads to more stable species and avoids thermal decomposition to copper zero and the unwanted symmetrical diene R(R')C=CH-CH=CR(R').[35] THF is best suited for the preparation of magnesium homo cuprates[36]



or unsymmetrical cuprates

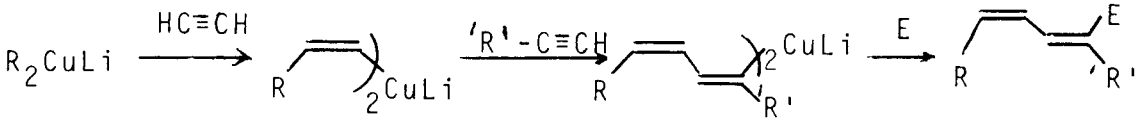


Z= OtBu, SPh, C≡C-R"

but the symmetrical homocuprates insert only one mole equivalent of alkyne, so that a vinyl alkyl cuprate results, in which the Csp_3-Cu bond is more reactive than the Csp_2-Cu bond, towards usual electrophiles, and the synthetic use of them is accordingly troublesome. On the other hand, the saturated alkyl-alkoxy cuprates present no extra stabilization, as compared with the corresponding alkyl copper reagents.

3-3 Addition of alkenyl cuprates to alkynes

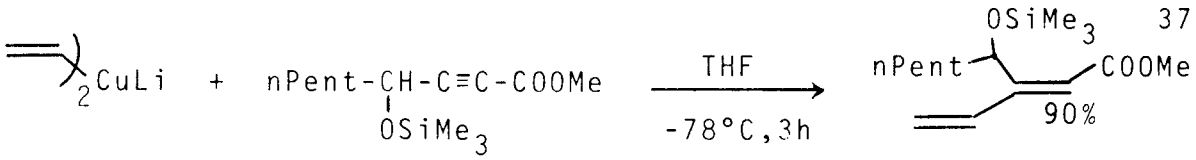
One of the easiest way to construct a conjugated diene system would be the addition of an alkenyl copper or cuprate derivative to the triple bond of an appropriate alkyne, leading to the formation of a dienic copper or cuprate reagent, which may react further with an electrophile :



However, among the organo-copper or cuprate reagents, the methyl-, aryl-, and alkenyl-copper are the less reactive ones as compared to their alkyl counterparts, for the carbocupration reaction.[33] Thus, only reactive alkynes are suitable substrates. In fact, many alkynes may react under appropriate conditions and only the non-functionalized mono- or bisubstituted alkynes are totally inert towards alkenyl copper reagents.

3-3-1 Acetylenic esters

Acetylenes bearing a conjugated carbonyl function, such as esters, ketones or aldehydes are, of course, very prone to add a cuprate reagent. This reaction may also be viewed as a conjugate addition to the ynone system ; the examples reported in the litterature include reactions with mono or bisubstituted esters :



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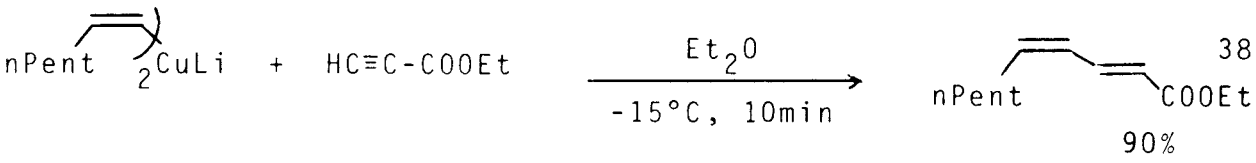

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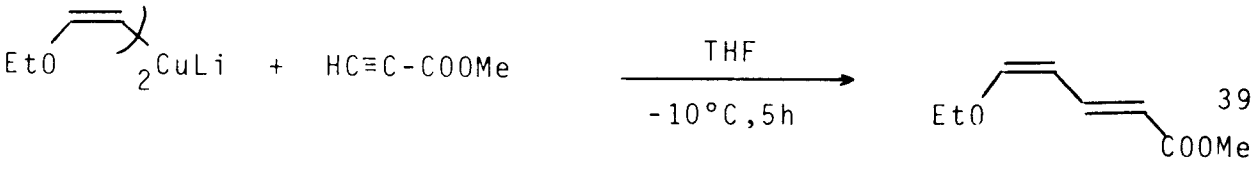

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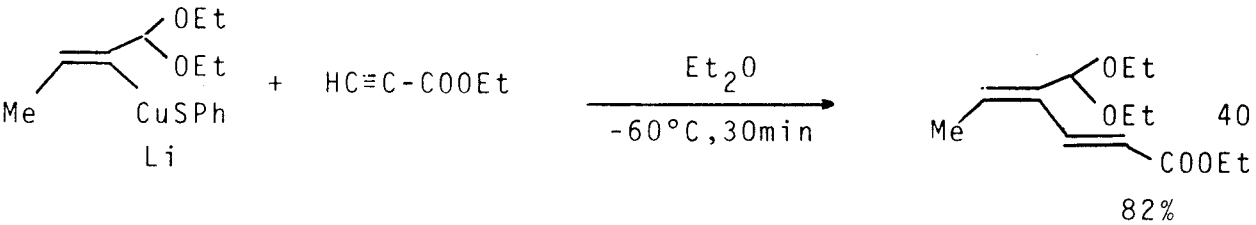

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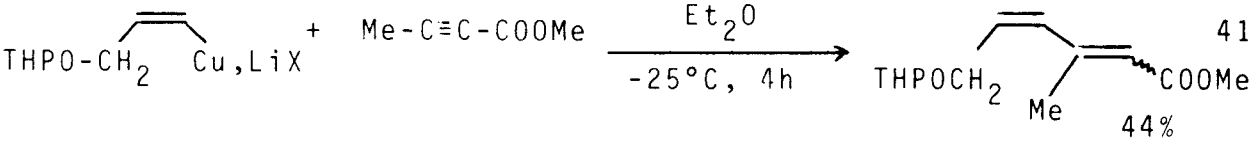

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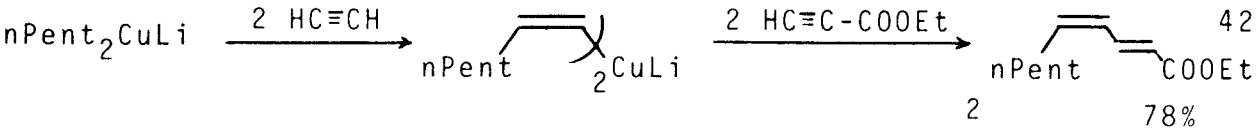
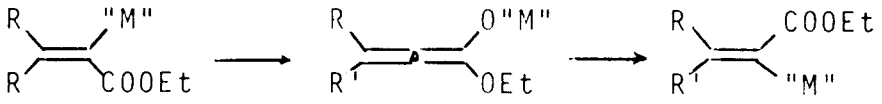
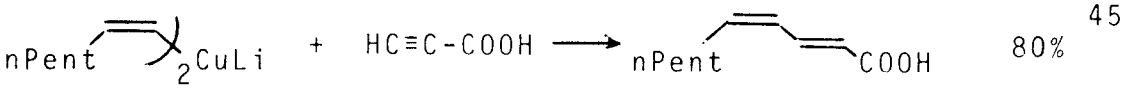
In these examples only half of the cuprate reagent was used. However, with the particularly reactive propiolic ester, both alkenyl groups may add :

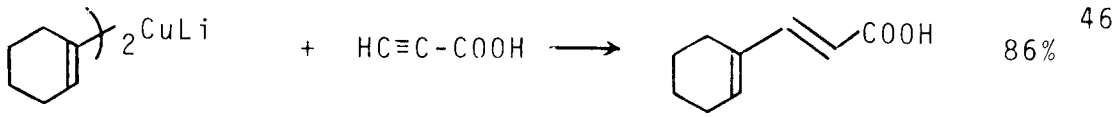


2(E)-4(Z)-Ethyl decadienoate, which is obtained in a 95% E-Z purity, is the major component of Bartlett's Pear aroma.[43] The stereochemical purity of the conjugated dienes obtained by this way is high enough but care should be taken to the experimental conditions, because of the facile isomerisation via the corresponding allenolate.[44]



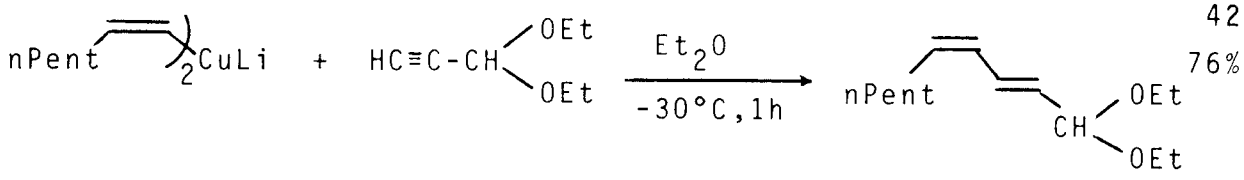
The best results are obtained in tetrahedrofuran (THF) solvent. An alternative is also to use the acid instead of the ester :

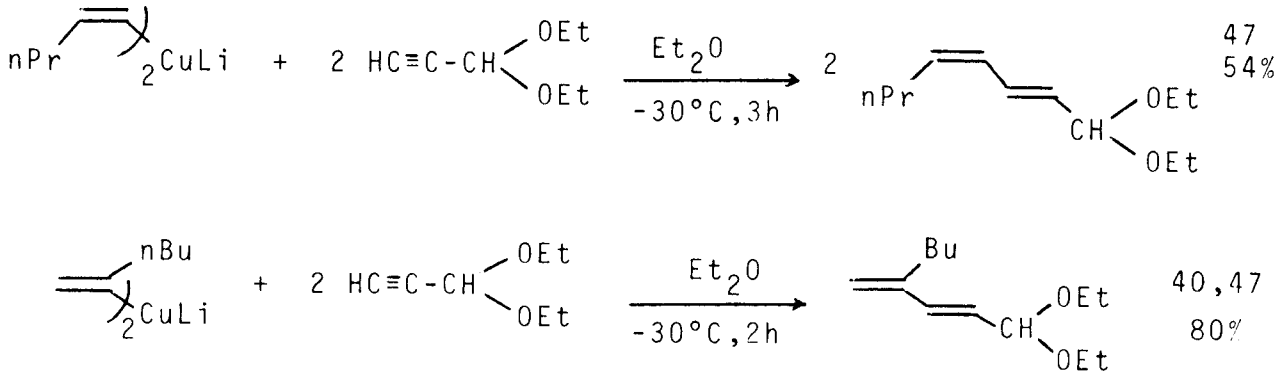




3-3-2 Acetylenic acetals

Acetylenic acetals and ketals, although less reactive than the corresponding esters are also prone to add alkenyl cuprates. However, only mono-substituted alkynes of this type can be used :



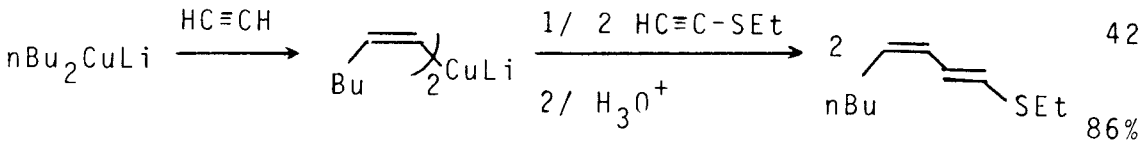


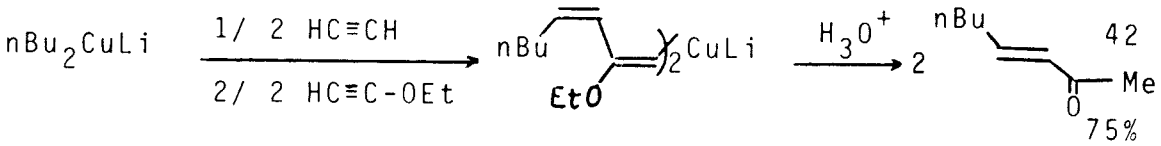
β(Z)-Monosubstituted alkenyl cuprates transfer well one of the two alkenyl groups, the second one being incompletely transferred. On the other hand α-mono-substituted cuprates (which are more reactive) transfer their two alkenyl groups.

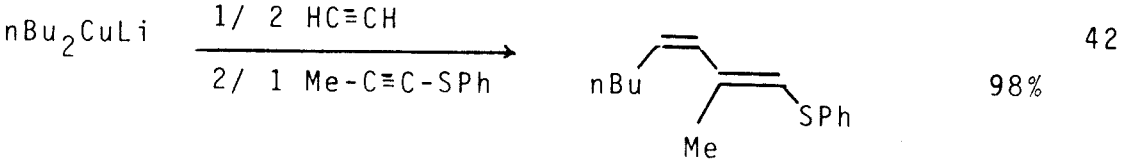
In contrast to the esters, there isno possibility to isomerise the dienyl cuprate in these cases, and the stereochemical purity of the dienes is almost 100%.

3-3-3 Heterosubstituted alkynes

Acetylenes bearing an heteroatom directly linked to the sp carbon atom may react with one or whith the two alkenyl groups of the cuprate, depending on their degree of substitution :

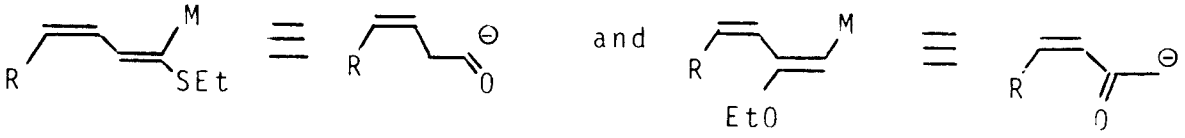






In this last case, the bisubstitution of the alkyne moiety allows only one alkenyl group to react. The opposite regio-selectivity observed, according to the heteroatom positionned

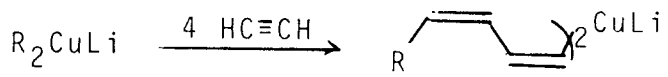
on the starting acetylene, leads to the formation of an alkenyl carbenoïd species (use of sulfur) or an E-β alkoxy alkenyl cuprate (in the case of oxygen) which are respectively equivalents of acyl anions or enolates of ethylenic ketones :



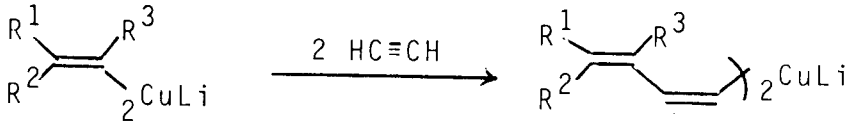
These heterosubstituted dienes are also useful building blocks of Diels-Alder reaction[48], where the stereochemistry of the diene system determines the substitution pattern of the cyclohexene ring.

3-3-4 Acetylene

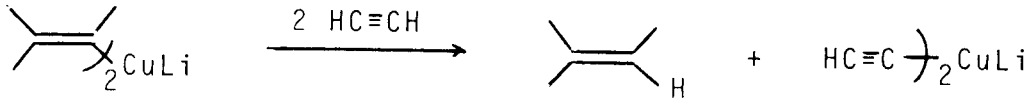
Acetylene itself is also reactive enough to allow carbocupration. It is also the more versatile for synthetic purposes. In the normal carbocupration of acetylene with dialkyl cuprates[49] we observed that under particular conditions the following bis-carbocupration proceeds to some limited extent



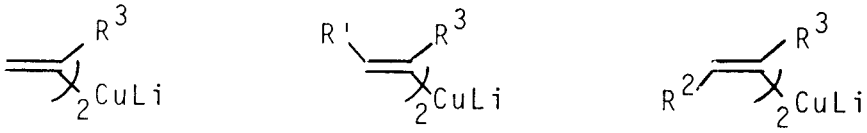
We were thus led to a systematic study of the addition of alkenyl cuprates to acetylene, according to their structural features, namely the degree of substitution of the sp_2 carbon atoms :



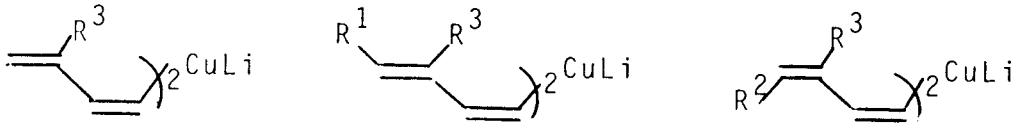
Since the temperature of addition is now higher than that which is required in the case of dialkyl cuprates addition, the results are highly depending upon the thermal stability of the starting alkenyl cuprate and the resulting dienyl cuprate. A notable side reaction which is also observed in some cases is the metallation of acetylene due to its two acidic hydrogens :



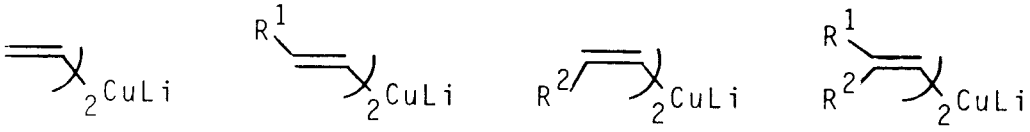
It turns out that the presence of the R^3 group, geminated to copper is essential for the success of the carbocupration, so that the reagents of type :



do insert smoothly two equivalents of acetylene, leading respectively to reagents of type :

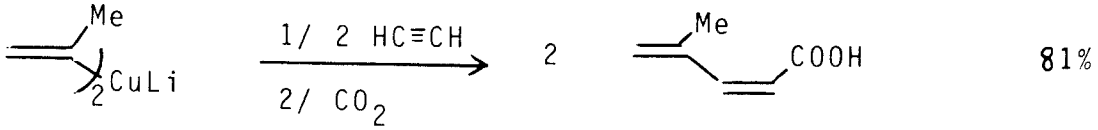


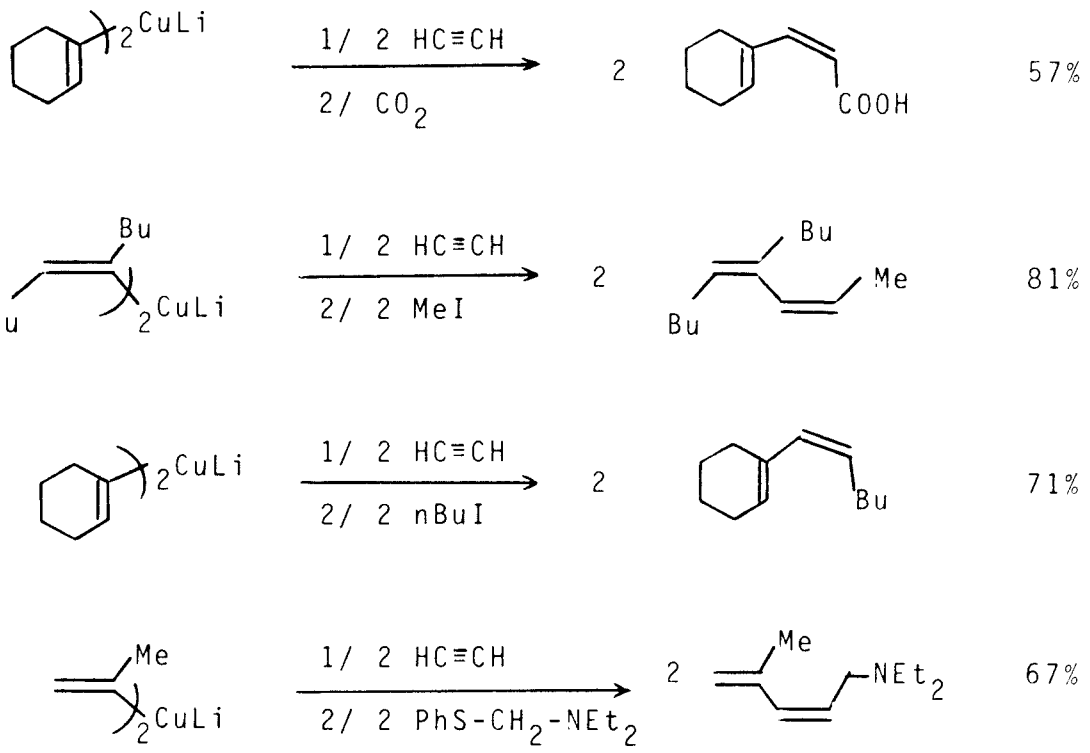
It is worthy of note that no further addition is observed, this fact may be tentatively assigned to an internal chelation of the copper atom by the former C=C bond. Reagents which do not bear the R^3 group, such as the following :



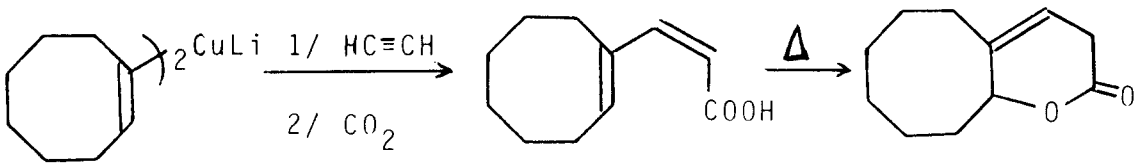
do also add acetylene, but the yields are, at present, disappointingly low (10-50%).

The dienyl cuprates obtained in this manner may be further used for chain elongation.[46] They behave, in fact, as normal alkenyl cuprates in their reactions with electrophiles. Thus, they have been carbonated or alkylated or aminomethylated as shown below[46] :





These dienyl cuprates may be used also in reactions with other electrophiles such as enones or epoxides for various synthetic purposes. Particularly interesting are the cyclo alkenyl cuprates which add efficiently to acetylene, and which may lead, after condensation, with an electrophilic reagent, to cyclisations such as the following :



In summary, alkenyl cuprates derivatives, obtained via carbometallation (or not), are good precursors of conjugated dienes via their addition to acetylene or other alkynes, affording dienyl cuprates of given geometry which may introduce directly the dienyl synthon in more sophisticated structures.

3-4 Coupling between vinyl copper reagents and vinylic halides

Vinyl copper reagents react with saturated halides in the presence of hexamethyl phosphotriamide (HMPT) and triethyl phosphite, but are inert towards vinylic halides.[33] On the

other hand, lithium vinyl cuprates react very sluggishly with the latter substrates (yield 5-10%). As a general rule for the use of such organometallics, a low temperature is recommended, to avoid decomposition, and the desired coupling reaction must be fast enough so that the temperature may not exceed +5, +15°.

3-4-1 Starting from vinyl copper-magnesium halide reagents

We have shown that under palladium zero catalysis, vinyl copper reagents couple with 1-iodo-1-alkenes, in the presence of magnesium salts[50,51]

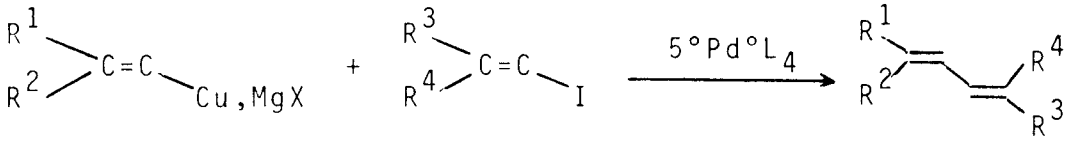
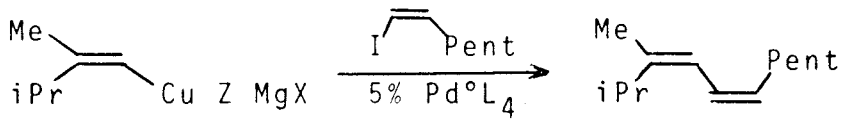


Table 1 shows that the 1-3 butadienes thus obtained, may be 1-mono- or 1,1-disubstituted with a large array of alkyl groups (primary, secondary, tertiary) or aryl groups. 1,1,4 tri- or 1,1,4,4-tetra-substituted ones may also be obtained with an excellent purity. Commercially available β-bromo styrene (90% E, 10% Z) may even be used stereoselectively; since Z-1-halo-1-alkenes react much slower than their E isomers, the corresponding diene is found 99.0% pure.

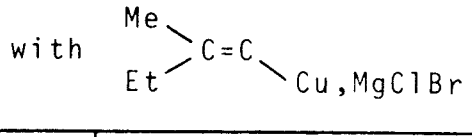
The use of hetero substituted vinyl cuprates present no synthetic advantage, as compared with the $ViCu,MgX_2$ reagent

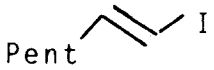
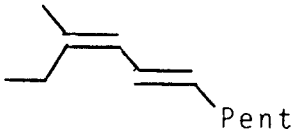
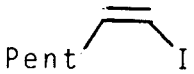
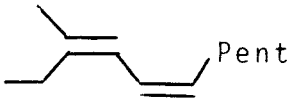
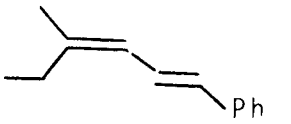
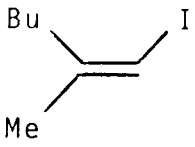
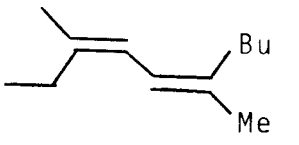


Z=X	Yield	64%	Purity	99.8 % Z,Z
Z=OtBu		60%		99.8 % Z,Z
Z=SPh		50%		99.5 % Z,Z

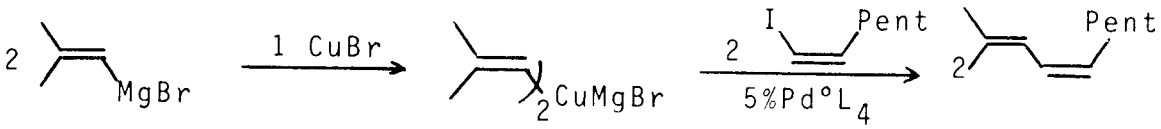
and the symmetrical magnesium divinyl cuprates cannot be obtained via carbocupration (as said above). However, these latter ones may be prepared (with some loss of isomeric purity) from the corresponding Grignard reagents.

Table 1 - Synthesis of dienes by the reaction of haloalkenes



1-halo alkene	Product	Yield %	Purity
		78	99.5 Z,E
		70	99.8 Z,Z
		74	99.0 Z,E
		55	99.8 Z,Z

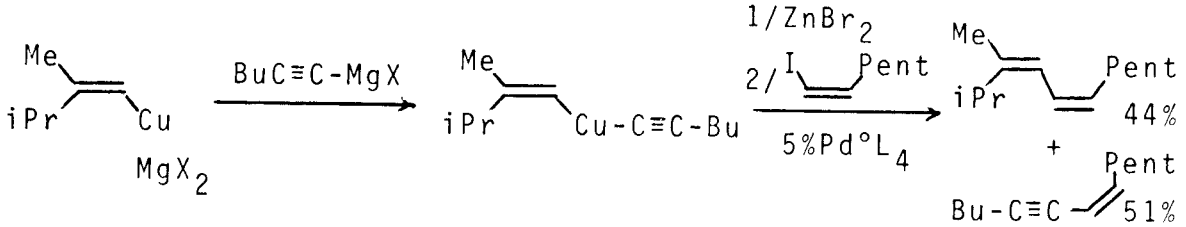
Their palladium catalyzed reaction with 1-iodo-1-alkenes is extremely slow, but becomes rapid in the presence of one equivalent (or less) of Zinc halides.



without $ZnBr_2$: yield 24%

with $ZnBr_2$: yield 94%

(Note that both vinylic groups have been converted to diene). The use of an ate complex derivatized from a magnesium acetylide proved unsuccessful :

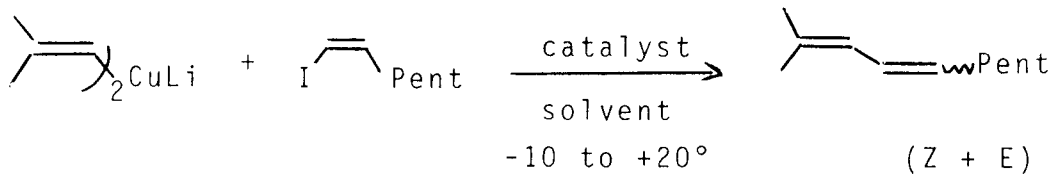


since transfer of the alkynyl moiety competes largely.

3-4-2 Starting from lithium cuprates[52]

This strategy is followed when 1-3 butadienes, mono substituted on carbon 1 are the target molecules.

Lithium divinyl cuprates react with 1-iodo-1-alkenes in the presence of Ni° or Pd° catalysts but yields and isomeric purity are low



Solvent	Catalyst	Time (h)	Yield %	Ratio Z/E
ether or THF	none	72	trace	
ether/THF	3%$NiBr_2(PPh_3)_2$	4	51	80/20
ether	5%$Pd(PPh_3)_4$	24	50	91/ 9
"	"	0.5	94[a]	97/ 3

a : inverse addition

except in the case of inverse addition of the cuprate to the haloalkene. However, in the presence of zinc halides a rapid reaction takes place and leads to high yields of diene, more than 99% pure. The reason must lie in the fact that the metal-metal exchange:

$$R_2CuLi + ZnX_2 \longrightarrow RCu + RZnX \xrightarrow{\not\ ZnX_2} 2\ RZnX$$

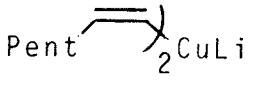
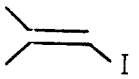
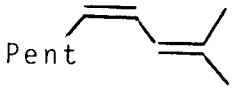
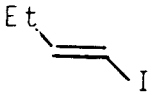
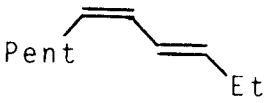
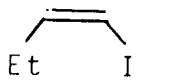
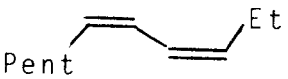
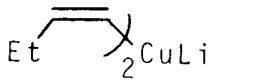
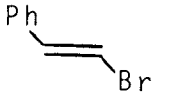
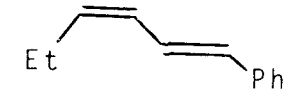
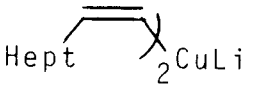
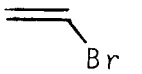
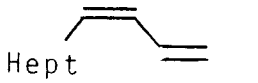
leads to a reactive Zinc species (The reverse reaction

$$Me_2Zn + CuX \longrightarrow MeZnX + MeCu$$

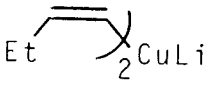
had been already disclosed by Thiele[53]).

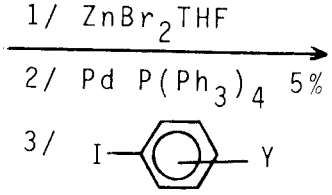
Some examples are presented in table II.

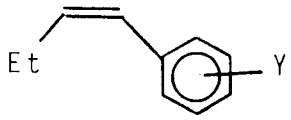
Table II - Coupling between lithium vinyl cuprates and 1-halo-1-alkenes in the presence of 5% $Pd(PPh_3)_4$ and 1 equivalent of $ZnBr_2$

Cuprate	Vinyl-X (purity)	Product	Yield %	Purity %
			94	99.8
"			80	98.9
"			86	99.5
			85	97.6
			91	99.8[a]

a : in the presence of HMPT, and of excess of bromo ethylene.

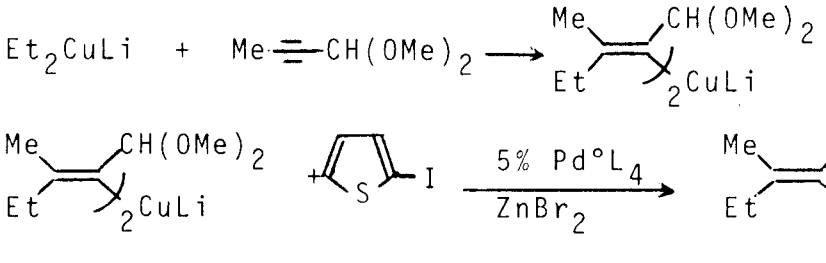
Table III - 





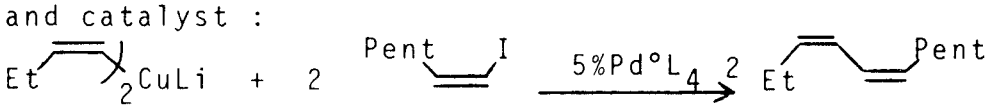
Y	Yield %
p.NO_2	80
p.OMe	65
H	67
p.Br	71
o.COOMe	72
p.COOMe	81

An extension of this study has shown that iodo arenes behave similarly : in the presence of zinc halides and a catalytic amount of $Pd^{\circ}L_4$, they couple efficiently with lithium divinyl cuprates to give β-substituted styrenes of Z geometry. The aryl ring may bear extra functionalities, like alkoxy, bromo, nitro, carbomethoxy groups, the electron with drawing substituents giving the fastest reaction (table III).[54] Heterocyclic substrates, as functionalized cuprates, behave as well[54]



The amount of zinc halides may be less than one equivalent (0.5, 0.25 and 0.05 equivalents have been used) but the velocity decreases accordingly.

In these reactions leading to dienes or styrenes, it should be pointed out that the yields were calculated from the cuprate reagent (or the haloalkene in a 1/1 ratio) : only one vinyl moiety is transferred. This may be inconvenient when a more sophisticated cuprate is used. The metal-metal exchange, leading from the lithium cuprate to a reactive vinyl zinc halide, and an unreactive vinyl copper - lithium halide reagent, the latter remains unchanged. However we have seen (3-4-1) that the vinyl copper - magnesium halide reagent is indeed reactive towards 1-iodo-1-alkenes. It turns out that vinyl copper - lithium halide reagents are also converted to reactive species if magnesium halides are added to the reaction mixture. Following these lines, it is then possible to use both vinyl moieties of a lithium cuprate, if (i)MgX_2 salts and (ii)ZnX_2 salts are added prior to the halo alkene and catalyst :



with $ZnBr_2$ alone, the yield is 84% for one butenyl moiety transferred, whereas with $ZnBr_2$ and $MgCl_2$ the yield raises to 84% for two transferred butenyl moieties.

3-5 Coupling between vinylic copper species and 1-halo-1-alkynes

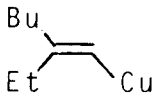
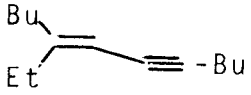
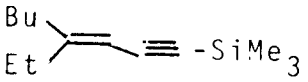
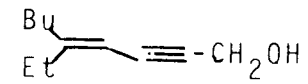
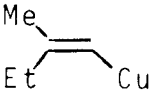
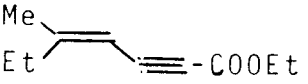
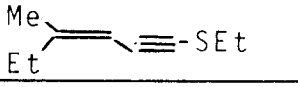
3-5-1 Starting from a vinyl copper-magnesium halide reagent

We have shown that the direct coupling between vinylic copper reagents and 1-halo-1 alkynes in ether may lead to a variety of products :

$$ViCu + RC{\equiv}C\text{-}X \longrightarrow Vi\text{-}C{\equiv}C\text{-}R + Vi\text{-}Vi + RC{\equiv}C\text{-}C{\equiv}C\text{-}R \ldots$$

resulting from metal/halogen exchanges. However the presence of THF and of tetramethylethylen diamine (1,2 to 2 equivalents) suppresses these side reactions so that the desired Z enyne is obtained in good yields[55,56]

Table IV - $R\text{-}C{\equiv}C\text{-}X + ViCu \longrightarrow R\text{-}C{\equiv}C\text{-}Vi$

ViCu	R-C≡CX	Product	Yield %
	n.Bu-C≡C-I		77
	n.Bu-C≡C-Br		78
	n.Bu-C≡C-Cl		8
"	$Me_3SiC{\equiv}C\text{-}I$		82
"	$THPO\text{-}CH_2\text{-}C{\equiv}C\text{-}Br$		80[a]
	EtOCO-C≡C-Br		78
"	EtS-C≡C-Br		82

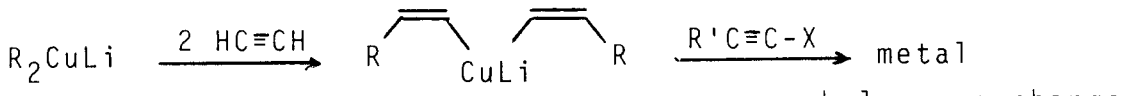
a : yield in alcohol after acidic treatment

1-bromo- and 1-iodo-1-alkynes behave similarly but 1-chloro give poor results.

As shown in table IV, the acetylenic moiety may bear a variety of functions, and use of trimethyl silyl halo-acetylene allows the preparation of terminal enynes after basic treatment.

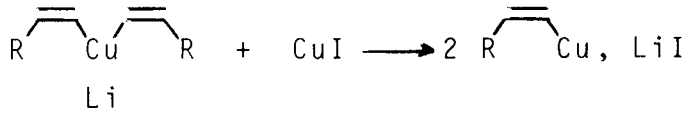
3-5-2 Starting from lithium cuprates[57]

The access to Z-β-monosubstituted vinyl copper species being quantitative from the lithium cuprates and acetylene, we choose this way to prepare Z enynes

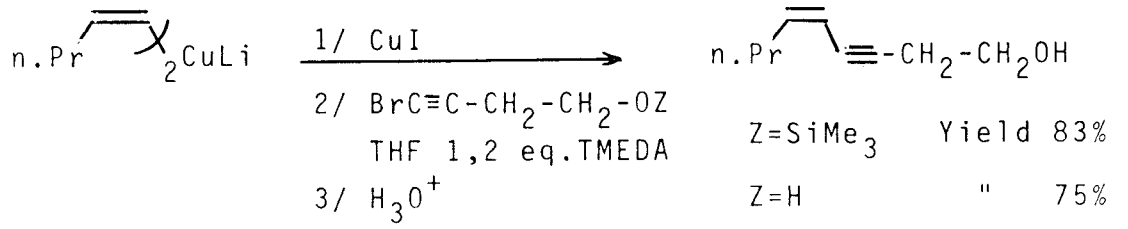


but only the undesired metal-halogen exchange took place.

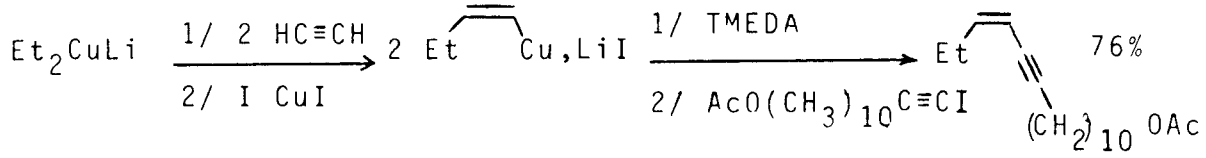
It is possible however to add one equivalent of copper halide to the divinyl cuprate :



and to couple the vinyl copper reagent, thus formed, in the presence of TMEDA with 1-halo-1-alkynes : the reaction is so fast that even halo alkynes bearing a free hydroxyl group may be used :

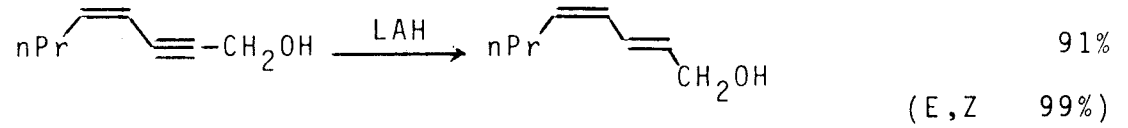


As an example, we prepared the pheromone of the processionary moth Thaumetopoea pityocampa according to this procedure [58]

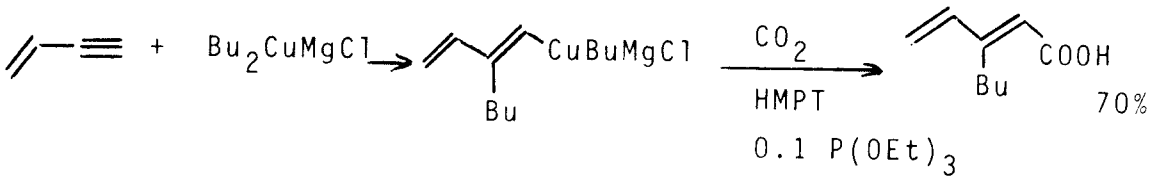


3-5-3 Transformation of enynes to dienes

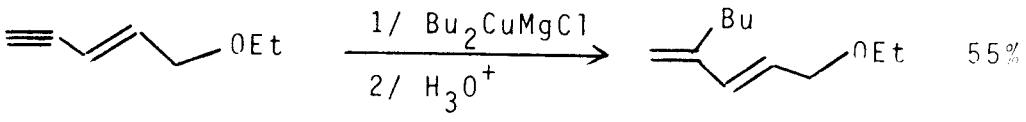
The reduction of the propargylic en-yn-ols (prepared according to the above procedure) by lithium aluminium hydride in boiling THF only affects the triple bond and represents an easy way to 2(Z), 4(E) alkadien-1-ols[55]



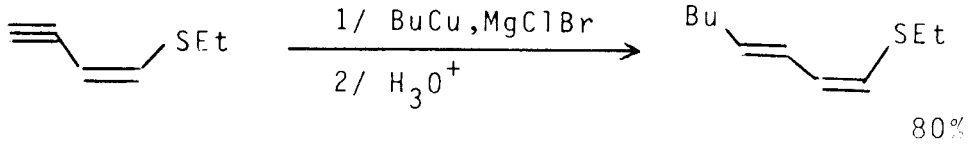
It is also possible to add alkyl copper reagents to conjugated enynes : the addition is exclusively of 1,2 type, and leads to alkylated butadienes[59,60] :



Hetero substituted enynes may be used as substrates, with the usual regioselectivity :



or the "reverse" regioselectivity :



CONCLUSION -

Organo copper reagents may be considered as good candidates for the elaboration of conjugated 1-3 butadienes, bearing substituents on carbon 1,2,3 or 4.

The vinyl-vinyl coupling presents a large scope since a large variety of vinyl copper may be derivatized from acetylene or terminal alkynes. The Z 1-iodo-1 alkenes are easily prepared from vinyl cuprates by iodonolysis;the E ones derive from other sources (hydroalanation, boration ...). The other main pathway, namely the addition of a vinyl copper species to an alkyne, is even more promising since a dienyl metal reagent is thus obtained, which may undergo further transformations. This latter aspect is actively studied in our laboratory.

This survey should help to keep in mind, how important is the selection of the various kinds of organo copper reagents, the selection of the main group metal salts, and the nature of the solvent.

ACKNOLEDGEMENTS -

The authors thank all the research staff of the Laboratory of Chimie des Organoéléments whose work is reported here, and for financial help from the C.N.R.S. The manuscript was typed by Mrs J. Mathé who is warmly thanked for her skill and her patience.

4 - EXPERIMENTAL PART

4-1 Preparation of alkenyl copper and cuprates reagents

Alkenyl cuprates which are not prepared by carbocupration of an alkyne, are prepared by addition of the corresponding alkenyl-lithium reagent (2 eq.) to a suspension of $CuBr.Me_2S$ complex (1 eq.) in ether solvent, at -30°C for an hour. A yellow greenish solution is obtained ready for further use.

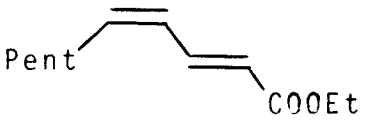
Lithium (Z) dialkenyl cuprates are prepared as follows :

to a suspension of purified copper iodide (28 mmol) in 70 ml ether, at -40°C, is added an ethereal solution of alkyl lithium reagent (50 mmol). After 30 min a blue solution of dialkyl cuprate is obtained. Acetylene gas (1200 ml, 55 mmol) (the proper volume is measured in a water gasometer) is bubbled rapidly into the solution of dialkyl cuprate at -50°C. The solution becomes green, while the temperature is raised at -25°C for 30 min. (Z) dialkenyl cuprates are ready for further use.

ββ-Bisubstituted magnesium alkenyl copper reagents are prepared as follows:

To a suspension of purified copper (I) bromide (55 mol) or copper bromide dimethyl sulfide complex, in 80 ml ether, is added a solution of the appropriate alkyl magnesium halide in ether solvent, at -35°C. After stirring for 30 min a yellow precipitate of alkyl copper reagent is formed. An appropiate alkyne is added (50 mmol) and the temperature of the mixture is raised to -15°C for 2 h. A deep green solution of alkenyl copper reagent is obtained and is ready for further use.

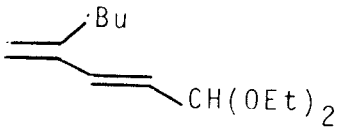
4-2 Ethyl (2-E), (4-Z) Decadienoate



To a solution of 25 mmol of (Z) diheptenyl cuprate (prepared from 50 mmol n.pentyl lithium reagent) are added 50 ml of THF at -50°C with cooling. Ethyl propiolate (25 mmol) is slowly added in solution in THF (15 ml) at -50°C (very exothermic). The reaction mixture which turns red, is

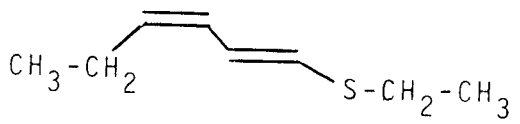
stirred 15 min at -30°C, then hydrolysed with 100 ml NH_4Cl sat. solution. 100 ml of hexane are added and the precipitate filtered off. The organic phase is washed one or two times with NH_4Cl sat. solution, dried over $MgSO_4$ and evaporated. The residue is distilled through a 15 cm Vigreux column to afford 4.4 g of pure Pear Ester. B.p. 81-82°/0.1 mmHg ; n_D^{20} 1.4881 ; IR (neat) cm^{-1} 1715 (COOEt), 1640, 1620 (C=C-C=C) ; ^1H NMR (CCl_4,δ) 7.22 (CH=,dd,1), 5.45-5.95 (CH=,m,3), 3.98 (CH_2-O,q,2), 2.13 (CH_2-C=q,2).

4-3 1,1 - Diethoxy4Butyl-2 E,4-pentadiene



To a solution of lithium di-1-hexen-?-yl cuprate (prepared from 50 mmol of alkenyl lithium) in 100 ml ether, at -40°C, is added an ethereal solution (15 ml) of 1,1-diethoxy propyne (50 mmol). The solution is stirred at -30°C for three hours, then hydrolysed with 80 ml NH_4Cl sat. solution and 20 ml 17% aqueous ammonia. The mixture is stirred at room temperature untill all precipitate dissolves. The layers are separated, the organic phase washed once with NH_4Cl sat solution, dried over K_2CO_3 and evaporated. The residue is distilled through a 15 cm Vigreux column. B.p. 55-66°/0.05 mmHg ; n_D^{20} 1.4563. IR (neat) cm^{-1} 3015, 1635, 940, 900. ^1H NMR (CCl_4,δ) 6.34 (CH-,d,1), 5.0-5.8 (CH=,m,3), 4.52 (CH_2-O,m,4), 2.22 (CH_2-C=,t,2).

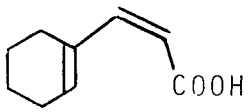
4-4 1-Ethylthio-1(E),3(Z)-Hexadiene



A solution of 25 mmol of (Z) dibutenyl cuprate is prepared in ether (from 50 mmol ethyl lithium). 80 ml of THF are added at -50°C, then 4.3 g (50 mmol) ethylthioacetylene in 20 ml THF. The mixture is stirred two hours at -5°C, then hydrolysed with 80 ml NH_4Cl sat. solution and 20 ml 20% aqueous HCl. After filtration, the organic phase is washed twice with NH_4Cl sat. solution, then dried over $MgSO_4$ and concentrated in vacuo. The residue is distilled to afford 6.12 g (86%) of the title compound. B.p. 82-84°/14 mmHg ;

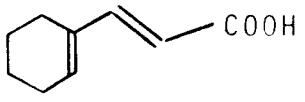
n_D^{20} 1.5373 ; IR (neat) cm^{-1} 3010, 1635, 1570 (HC=CH) ; ^1H NMR (CCl_4,δ) 6.35 (CH,dd,1), 6.05 (CH=,d,1), 5.86 (CH=, dd,1), 5.18 (CH=,d,1), 2.66 (S-CH_2,q,2), 2.13 (CH_2-C=,m,2).

4-5 3(Z)-1(1-cyclohexenyl) acrylic acid



An ethereal solution of cyclohexenyl lithium (prepared according to Braude[62]) (30 mmol) is added to a suspension of CuBr,Me_2S (16 mmol) in 70 ml ether at -30°C. After stirring for 30 min a pale green solution is obtained. The temperature is raised to 0°C and acetylene gas (675 ml, 33 mmol) is bubbled into the solution. The gas is absorbed and stirring is continued for 30 min at +20°C. The dark solution is cooled to -20°C, THF is added (50 ml), then HMPT (5.4 g, 30 mmol) and 100 mg $P(OEt)_3$ (as catalyst). Dry CO_2 is bubbled into the reaction mixture, which is allowed to reach room temperature. After stirring for three hours, the mixture is hydrolysed with 70 ml HCl 5N. After filtration the organic phase is washed twice with HCl 5N, then with dilute aqueous KOH. This basic aqueous phase is separated and acidified with dilute H_2SO_4. The acid is extracted twice with 50 ml portions of ether, dried over $MgSO_4$ and concentrated. The crude acid melted at 59°C and amounted to 2.6 g (57% yied). IR cm^{-1} 3050 (COOH) 1690, 1615 (C=C COOH) 920, 855, 820 (C=C-C=C) ; ^1H NMR ($CDCl_3$,δ) 6.61 (=CH,d,1) 6.23 (=CH,t,1) 5.76 (=CH,d,1) J_{cis} : 13 Hz ; ^{13}C NMR ($CDCl_3$,δ) 172.7 (COOH) 147.4, 137.2, 135.5, 115.0 (=CH).

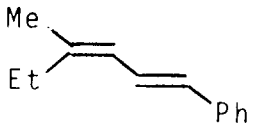
4-6 3 (E)-(1-Cyclohexenyl) acrylic acid



Lithium dicyclohexenyl cuprate is prepared as above (from 50 mmol) of lithium reagent and 27 mmol CuBr,Me_2S). Propiolic acid (25 mmol) is added in ether at -45°C. The mixture is stirred 30 min. at 0°C, then hydrolysed and worked up as above. 3.3 g of crude acid are obtained (86%) which melted at 109°. ^1H NMR ($CDCl_3$,δ) 7.62 (=CH,d,1) 6.44 (=CH,t,1)

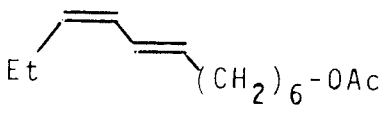
5.96 (=CH,d,1) J_{trans} : 17 Hz ; ^{13}C NMR ($CDCl_3$,δ) 173.5 (COOH) 150.7, 140.5, 135.0, 113.6 (=CH).

4-7 1-Phenyl, 4-Methyl, 1(E)-3(Z) Hexadiene



30 mmol of magnesium alkenyl copper reagent are prepared as described above. To this solution are added 50 ml THF at -20°C, then a mixture of 25 mmol β-bromo styrene (E/Z : 91/9 and 1.25 mmol of $Pd(PPh_3)_4$ in 20 ml THF. The reaction mixture is allowed to reach room temperature, stirred for 30 min., then hydrolysed with 80 ml NH_4Cl sat. solution. The organic phase is separated and concentrated in vacuo without drying. The crude product is diluted with 150 ml pentane to precipitate all organic salts, then filtered and washed once with NH_4Cl sat. sol. and aqueous NH_4OH, dried over $MgSO_4$ and the solvent evaporated. Distillation through a 10 cm Vigreux column afforded 3.2 g of pure product (74%). B.p. 73°/0.01 mmHg ; n_D^{20} 1.5985 ; IR (neat) cm^{-1} 3030, 3015, 1640, 1600, 960, 750, 690. ^1H NMR (CCl_4,δ) 7.09 (=CH,d,1) 6.47 (=CH,d,1) 6.01 (=CH,dd,1) 1.84 (CH_3,s,3).

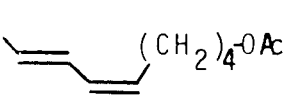
4-8 7 (E), 9(Z)-Dodecadien 1-yl acetate



To a solution of (Z) dibutenyl cuprate, (prepared from 6 mmol of EtLi in 30 ml ether, are added at -40°C 20 ml THF, then a solution of 700 mg $ZnBr_2$ in 10 ml THF. After stirring 30 min at -20°C, a mixture of 3 mmol 1-iodo, 1(E)-octen-8-yl acetate (94% E purity) and 0.15 mmol $Pd(PPh_3)_4$ in 10 ml THF is added. The reaction mixture is slowly warmed to +10°C and after 30 min at this temperature, 40 ml NH_4Cl sat. solution are added. The organic phase is concentrated in vacuo and 50 ml of pentane are added to precipitate the inorganic salts which are filtered off. The organic solution is washed twice with 20 ml NH_4Cl sat. solution, dried over $MgSO_4$

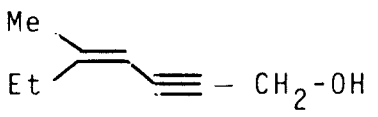
and the solvent removed in vacuo. The crude residue is purified by preparative T.L.C. to afford a 78% yield of pheromone (97% EZ purity). ^1H NMR (CCl_4,δ) 6.74 (dt,1) 6.25 (dd;1) 6.02 (dd,1) 5.38 (dt,1). ^{13}C NMR ($CDCl_3$,δ) 179.0 (-COO-) 134.3, 131.6, 128.1, 125.7 (=CH)

4-9 5(Z),7(E)-Tridecadien-1-yl-acetate



To a solution of 15 mmol of di-6-ethoxyethyl 1-(Z) hexenyl cuprate (prepared from 30 mmol of 4-ethoxyethyl butyl lithium) in 100 ml of ether, are added 30 ml THF at -30°C. Then, a solution of 30mmol $MgCl_2$ in 50 ml THF is added at the same temperature, followed (after 10 min) by a solution of 30 mmol $ZnBr_2$ in 20 ml THF. After stirring for 15 min a mixture of 30 mmol 1-iodo-1(E) heptene and 1.25 mmol $Pd(PPh_3)_4$ in 50 ml THF is added at -15°C. The reaction mixture is warmed slowly (30 min) to +15°C maintained one hour at this temperature, then hydrolysed with 80 ml NH_4Cl and worked up as described in 4-7. The crude product is acetylated by pouring into 30 ml of a mixture of AcCl in AcOH (1:10) at 40°C for twelve hours. After addition of 10ml pentane and washing with 30 ml $NaHCO_3$ sat. solution, the organic solution is dried on $MgSO_4$ and the solvents evaporated. The residue is distilled through a 10 cm Vigreux column to afford 3.7 g of the title product (52% yield). B.p. 85-87°/0.01 mmHg ; n_D^{20} : 1.4701 ; IR (neat) cm^{-1} : 3020 (C=C) 1745 (-COO-) 1645, 985, 950, 730 (C=C) ; ^1H NMR ($CDCl_3$,δ) 6.40 (=CH,dd,1) 6.04 (=CH, dd,1) 5.72 (=CH,dt,1) 5.38 (=CH,dt,1) ; ^{13}C NMR ($CDCl_3$,δ) 170.8(-COO-) 135.0, 129.5, 128.9, 125.6 (=CH).

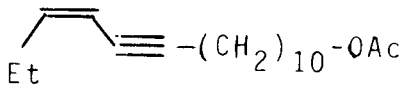
4-10 5-Methyl-4-Hepten-2-yn-1-ol



2-Methyl-1(Z) Butenyl copper, magnesium halide, is prepared (50 mmol) in 150 ml ether as described previously (see 4.1). 80 ml of THF and 100 mmol tetramethyl-

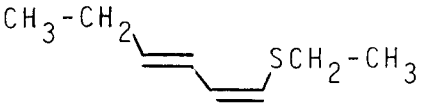
ethylene diamine (TMEDA) are added at -20°C and then a solution of 1-bromo-3-trimethylsiloxy-1-propyne in 20 ml THF. The green solution is discoloured in about 15-20 min and a white precipitate appears. After stirring for one hour at -10°C the mixture is hydrolysed with 80 ml H_2SO_4(2N), the salts are filtered off and the organic phase is diluted with 150 ml pentane. This phase is washed once again with 50 ml H_2SO_4(2N), then with 80 ml $NaHCO_3$ sat. solution, dried over $MgSO_4$ and the solvents are removed in vacuo. Distillation of the residue affords the title alcohol in 82% yield. B.p. 57°C/0.4 mmHg ; n_D^{20} : 1.5022 ; IR (neat) cm^{-1} 3320 (-OH) 2210 (C≡C) 1625 (C=C) 1015 (C-O) ; ^1H NMR (CCl_4, δ) 5.21 (=CH,s,1) 4.32 (-CH-O,s,2) 1.76 (CH_3,s,3).

4-11 <u>13-Hexadecen-11-yn-1-yl acetate</u>

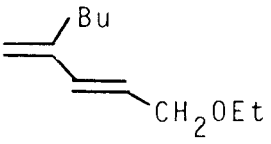


A solution of lithium di 1-(Z) Butenyl cuprate (50 mmol) is prepared in 180 ml ether as described previously (see 4-1) (from 100 mmol EtLi). To this reagent are successively added at -30°C, CuI (60 mmol), 100 ml THF and 18.5 ml TMEDA, whereupon all CuI was dissolved. A solution of 12-iodo-11-decyn-1-yl acetate in 30 ml THF is added dropwise and the stirred mixture is warmed to 0°C for 30 min. The mixture is then hydrolysed with 50 ml of ammonium chloride solution and 50 ml 2N hydrochloric acid, filtered on celite and partitioned. The organic phase to which 200 ml of hexane is added is washed successively with ammonium chloride solution, with 5% sodium thiosulfate, with 10% ammonium hydroxide, and with sat. sol. ammonium chloride again, then dried over magnesium sulfate and concentrated on a rotatory evaporator. The residue is distilled through a 15 cm Vigreux column to afford 12.6 g of pure pheromone (76%) yield. B.p. 105-107°/0.01 mmHg ; n_D^{20} : 1.4701 ; IR (neat) cm^{-1} 3020 (HC=CH) 2210 (C≡C) 1740 (OAc)

730 ($HC^{Z}=CH$) ; ^{1}H NMR (CCl_4,δ) 5.88 (=CH,dt,1) 5.47 (=CH,d,1) 4.12 (CH_2-O,t,2) ; ^{13}C NMR ($CDCl_3$,δ) 170.9 ($C\overset{O}{\leq}_{O}$) 143.7, 109.0 (C=C) 94.4, 77.3 (C=C) 64.6 (CH_2-O)

4-12 1-Ethylthio,1(Z)-3(E)-Hexadiene 

50 mmol of ethyl copper are prepared in 100 ml ether from copper bromide and ethyl magnesium bromide at -35°C. To this yellow suspension are added 50 mmol of 1-ethylthio-1-buten-3-yne (prepared according to ref. 63) in 20 ml ether, at -40°C. The reaction mixture is stirred at -20°C for two hours, then hydrolysed with 50 ml NH_4Cl and 30 ml HCl 5N, filtered and washed twice with NH_4Cl sat. solution. The organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is distilled to afford 5.8 g of product (82%). B.p. 87°/15 mmHg ; n_D^{20} : 1.5331 ; IR (neat) cm^{-1} 3010, 1640, 1570, 970 ; ^{1}H NMR (CCl_4,δ) 6.29 (ddt,1) 6.04 (t,1) 5.77 (d,1) 5.64 (dt,1).

4-13 1-Ethoxy-4-n butyl-2(E),4-pentadiene 

To a suspension of 25 mmol CuBr in 50 ml THF are added 50 mmol of a THF solution of butyl magnesium bromide, at -50°C. After stirring for two hours at this temperature, 1-ethoxy-2(E)-penten-4-yne (25 mmol) in 20 ml THF is added and the reaction mixture is kept at -40°C for two hours, then hydrolysed with 80 ml HCl 5N. 100 ml hexane or pentaneare added and the organic phase is washed twice with NH_4Cl sat. solution, dried over $MgSO_4$ and concentrated in vacuo. The residue is distilled to afford 2.3 g (55%) of pure product. B.p. 42°/0.05 mmHg ; n_D^{20} : 1.4607 ; IR (neat) cm^{-1} 1610, 1105, 970, 890 ; ^{1}H NMR (CCl_4,δ) 6.2 (=CH,d,1) 5.71 (=CH,dt,1) 4.94 ($=CH_2$,s,2).

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