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PALLADIUM MEDIATED SYNTHESIS OF CONJUGATED E or Z ENONES AND UNSYMMETRICAL DIVINYL KETONES. ONE-POT PREPARATION OF ISOEGOMAKETONE

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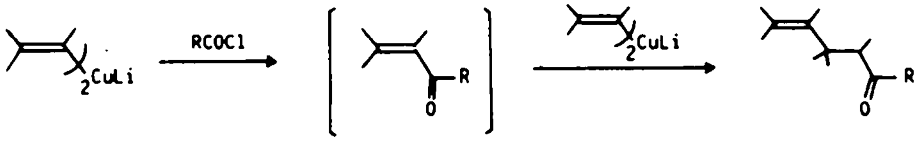
Abstract -The palladium (o) catalyzed coupling of acyl halides or anhydrides with alkenyl copper reagents furnishes γ,β ethylenic ketones and α,β-α',β' diethylenic ketones in high yield. The substitution pattern of the alkenyl copper reagent, directly obtained by carbocupration of alkynes, is fully retained. Anhydrides of Z-ethylenic acids also retain their Z stereochemistry. β-halogeno-vinyl ketones react under the above conditions to afford $\alpha\beta$-γ,δ dienones. An efficient one-pot synthesis of Z or E isoegomaketone is reported.

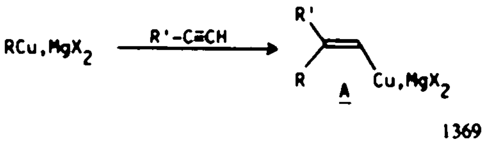
INTRODUCTION -

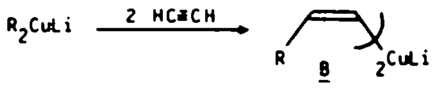
Among the various approaches to the synthesis of conjugated enones, the acylation of organometallic reagents is probably the most direct one[1]. The main limitation to this concept is the reactivity of the organometallic reagent towards the newly formed ketone, which has to be less reactive than the acylating agent. Nevertheless, a plethora of methods are available based either on an especially reactive acyl derivative[2], or on a new organometallic reagent[3]. Concerning this latter approach, the acylation of organocopper derivatives is considered as one of the best ways for the synthesis of ketones[4].

In the case of alkenyl copper or cuprate reagents, however, this method suffers from a serious drawback : the conjugate addition of the cuprate to the newly formed ketone[5] :

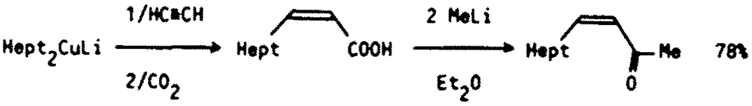


It was our goal to use the alkenyl copper A and cuprate reagents B, obtained by carbocupration of alkynes[6], to the synthesis of α,β-ethylenic ketones with a stereodefined substitution pattern





Especially, the synthesis of conjugated enones of pure Z configuration is not an easy task as judged by a brief survey of the litterature[7]. Moreover, they are known for their strong tendency to isomerise into the more stable E isomer, by simple heating or in the presence of trace amounts of acid[1]. Although we had prepared such a Z enone according to :



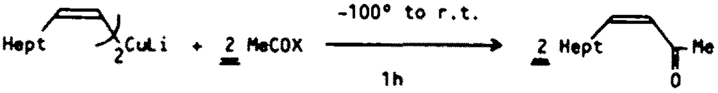
This method is limited to methyl ketones[2b].

We report, herein, the results of our investigations in the field of the synthesis of such ketones.

MONOETHYLENIC KETONES

Alkenyl copper reagents A are not very reactive towards acyl halides and a 25-35% yield of isomerized ketone is usually obtained[8]. No conjugate addition to the obtained, strongly hindered enone, is either observed. On the other hand, cuprates B are very reactive and the main product, obtained in Et_2O or THF solvent, was the readdition product to the enone (see table 1). However, when the reaction was performed with a strongly polar cosolvent, such as HMPT (4 eq.), in order to enhance the rate of acylation[4b] and to slow down the rate of the undesired conjugate addition[9], a moderate to good yield of non-isomerised ketone was obtained. Acetyl chloride was clearly less reactive than acetyl bromide (compare entries 2 and 3) which was able to cleave the THF ring, the homogenizing cosolvent[10], even at a low temperature. The use of tetrahydropyran in its place allowed an optimal yield of 60%, based on the use of both alkenyl groups of the cuprate (entry 4).

TABLE 1 -

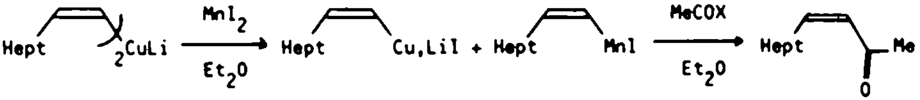


Entry	X	Solvent/cosolv.	Yield [a]	Z purity
1	Cl	Et_2O or Et_2O/THF	10 %	70 %
2	Cl	Et_2O/THF/HMPT (4eq)[c] (70:30)	31 %	97 %
3	Br	Et_2O/THF/HMPT (4eq) (70:30)	44 %	97 %
4	Br	Et_2O/THP[d]/HMPT (4eq) (70:30)	61 %	98 %

a : yields of isolated ketone, based on both alkenyl groups of the cuprate
b : determinated by gas chromatography on capillary glass column (OV101, 25m)
c : HMPT : hexamethyl phosphoric triamide $OP(NMe_2)_3$. Four equivalents per acid halide
d : THP : tetrahydropyran

Other combinations of cosolvents (Me_2S, DMSO, DMF, Pyridine) or acylating agents (anhydrides, thioesters, acid fluorides) met with less success, either because of a low yield, or isomerisation of the Z enone, or the predominance of side reactions (pyridine[11]). It should be mentioned, however, that a recent publication reported that selenoesters were very efficiently coupled with alkenyl copper reagents[12]. (Only one alkenyl group is used however).

An improvement of the desired coupling was then sought through transmetallation of the alkenyl cuprate derivative to a more efficient organometallic reagent such as the organomanganese ones[3g]

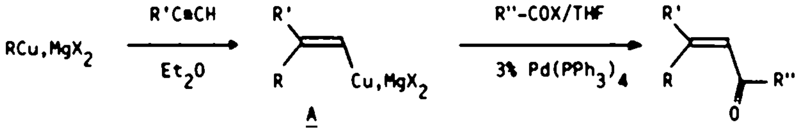


X : Cl 32% Z purity >94%
X : Br 61% " > "

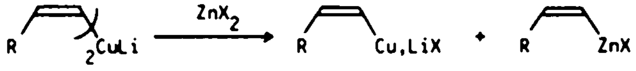
Although the yield is quite acceptable with acetyl bromide, it is a low one based on both alkenyl groups of the cuprate (30%).

Among the various acylation methods, the transition metal catalysed ones (Fe^{13}, Ni^{14}, Pd^{15}) attracted our attention, since we knew from previous studies that alkenyl copper derivatives undergo Pd° catalysed reactions, such as the coupling with alkenyl and aryl halides.[16]

We found that alkenyl copper reagents, associated with magnesium salts A are also acylated in the presence of Pd° catalyst to afford the desired α,β-ethylenic ketone with a stereodefined substitution pattern

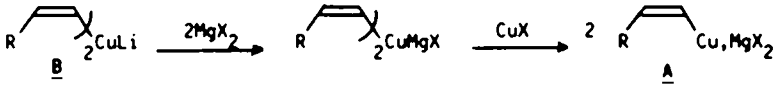


In the case of lithium dialkenyl cuprate B, many alternatives are possible to accomplish successfully this acylation. One of them consists in the transmetallation of this organometallic reagent into the zinc species[16] which is known to be efficiently acylated under Pd° catalysis[13i,j] (entries 5 and 6, Table II).



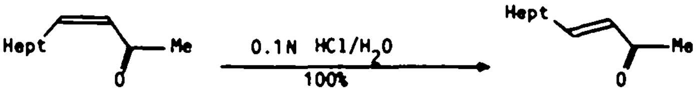
B

Another possibility, which has the advantage of using both alkenyl groups of the Z dialkenyl cuprate, is to transform this species into two equivalents of Z alkenyl copper reagent, associated with magnesium salt, by addition to the lithium cuprate of two equivalents of magnesium halide followed by addition of one equivalent of copper halide (entry 7).



As shown in Table II, alkenyl copper reagents A react with a great variety of acyl chlorides, to produce variously substituted conjugated enones in high yield. The substitution pattern of the alkenyl copper reagent is fully retained, as judged by gas chromatography on capillary glass column (OV1, 25m). In all the examined cases the stereoisomeric purity is exceedingly high (>99%). Palladium catalyzed isomerisation of such enones is observed only at high temperature (refluxing THF) for prolonged periods.[15e]

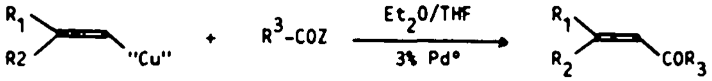
It should be recalled that it is very easy to isomerise these ketones by dilute acid[17] and, thus, to have both isomers for comparative purposes. It is interesting to note that, in contrast to α,β-disubstituted enones 4-8, Z-mono-substituted enones 1-3 are completely isomerized into the E ones :

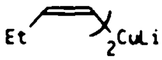
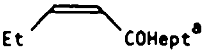
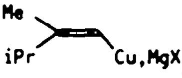
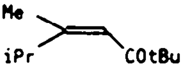
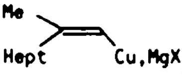
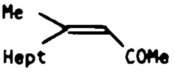
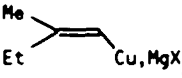
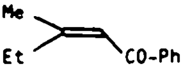
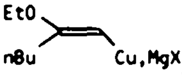
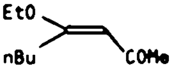
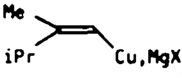


1Z >99% 1E >99%

Thus, our method may afford either the Z or E ethylenic ketone in high yield.

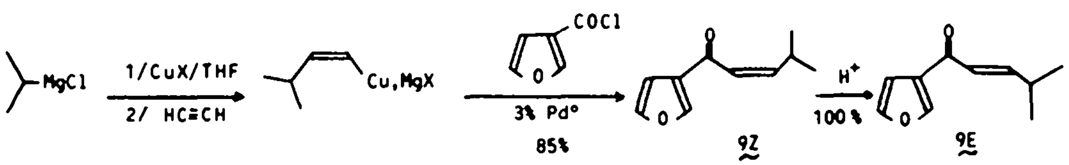
Table 11 -



Entry	Organocopper reagent	Acylating agent	Product	Isolated yield
5		MeCOCl (ZnBr$_2$)	 [a] 1Z	80 %
6		HeptCOCl (ZnBr$_2$)	 [a] 2	85 %
7		nBuCOCl (+ 2MgCl$_2$) (+ 1CuBr)	 [b] 3	76 %
8		tBuCOCl	 4	84 %
9		MeCOCl	 5	70 %
10		PhCOCl	 6	73 %
11	"	PhCOO-COOEt	" 6	80 %
12		MeCOCl	 7	74 %
13		Cl-COOEt	 8	56 %

a : only one alkenyl group used
b : both alkenyl groups enter into reaction

This possibility of obtaining, at will, the E or Z enone is exemplified by the following one-pot synthesis of isoegomaketone 9E, a natural fragrance from Perilla Frutescens[18]. This synthesis compares very well with previous ones[19] in efficiency, as well as in simplicity :



9Z 9E

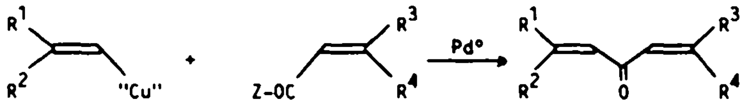
Addition of acetylene to isopropylcopper reagent produced the Z-alkenyl copper derivative which was directly coupled with 3-furoyl chloride, in the presence of 3% Pd(PPh_3)$_4$. The obtained unnatural Z-isoegomaketone 9Z (85% isolated yield) is readily isomerized quantitatively to pure E-isoegomaketone 9E. Interestingly, the odour of the unnatural Z isomer was much more pleasant than that of the natural E one.

In general, any alkenyl copper reagent generated by carbocupration may be used in our ketone synthesis : non functionalized as well as functionalized ones, such as the one bearing an enol ether functionality (Table II, entry 12). On the other hand, the reaction with ethyl chloroformate, although less efficient, provides an easy entry to α-β ethylenic esters with a known substitution pattern (Table II, entry 13).

Another interesting feature in this series, is the possibility to use mixed carbonic-carboxylic anhydrides instead of acid chlorides . These anhydrides are a useful alternative for the cases where the acid chloride cannot be prepared from the corresponding acid (vide infra). This is the first report on acylation with these anhydrides under Pd° catalysis.

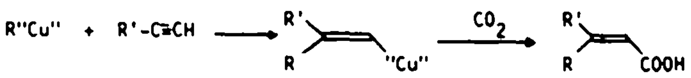
DIETHYLENIC KETONES

A conceivable extension of our ketone synthesis is its application to the preparation of unsymmetrical divinyl ketones.

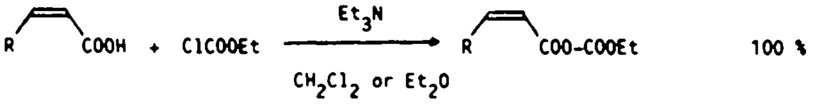


Such ketones are important synthetic intermediates. For example, the Nazarov cyclisation reaction[21] provides an easy entry to variously substituted cyclopentenones, and therefore to many five-membered ring natural products.

A number of methods exists for the synthesis of divinyl ketones, all with their scope and limitations[22]. Our aproach is based on the easy availability of α-β unsaturated acids, precursors of the acid chlorides or the mixed anhydrides. One of them, based on the carbonation of alkenyl copper reagents, provides these acids with a know substitution pattern[23] :



Acid chlorides of E ethylenic acids are readily prepared in the pure form[24]. On the other hand, Z ethylenic acid chlorides are usually isomerised during their preparation. In this case the use of the mixed anhydrides is largely emphasized since they are easily prepared without any isomerisation[25].

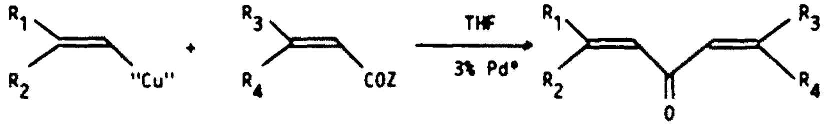


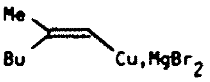
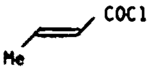
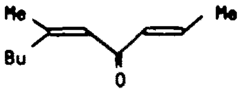
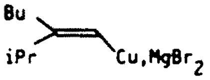
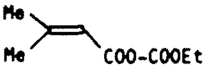
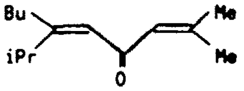
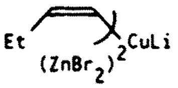
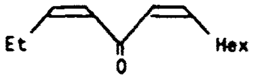
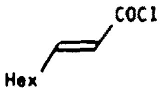
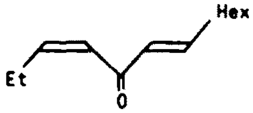
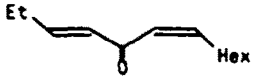
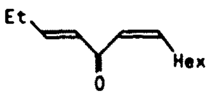
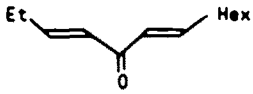
As shown in Table III, the reaction of alkenyl copper reagents A with ethylenic acid chlorides or mixed anhydrides affords the unsymmetrical divinyl ketones in high yield and with complete stereochemical control (> 99%). Thus, the four possible stereoisomers of 3,6-tridecadien-5-one have been synthetized. They are clearly separated by gas chromatography and the ^{13}C NMR spectrum of a mixture of them all, displays 16 isolated sp2 carbons. Ketones 12Z,Z, 12Z,E and

12E,Z are very prone to isomerisation into their **12E,E** isomer and all attempts to isolate them by column chromatography or distillation resulted in partial isomerisation. Nevertheless the crude ketone is sufficiently pure for further uses in synthesis.

Finally, it should be pointed out that mixed carbonic-carboxylic anhydrides may be used with organometallic reagents other than organocopper ones, such as organozincs (entry 18) and probably with any other ones which undergo Pd° catalyzed reactions.

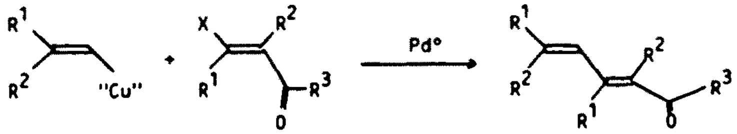
Table III -



Entry	Organometallic reagent	Acetylating agent	Product		Yield(a)
14				**10**	100 % (85 %)
15				**11**	92 % (58 %)
16				**12Z,Z**	87 %
17	"			**12Z,E**	88 %
18				**12E,Z**	94 %
19		$\xrightarrow{H^+}$		**12E,E**	100 %

a : Isolated yields in parentheses

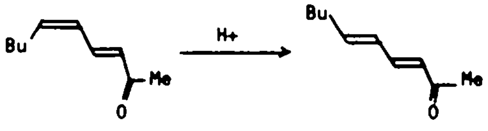
Another extension of our ketone synthesis is the obtention of α,β-γ,δ dienones for which few preparations are available.[7e,26]



Acyclic as well as cyclic β-halogeno vinyl ketones are well known compounds and their preparation is very convenient and high yielding[27].

These β-halogeno vinyl ketones may be considered as vinylogues of acyl halides, and as such, they should also react, under Pd° catalysis. Dialkyl cuprates derivatives are already known to react with these halides[28], a reaction which can be viewed as a conjugate addition reaction, followed by elimination of copper halide.

However, alkenyl copper reagents are not reactive enough, and they decompose thermally before any coupling occurs. Only β-iodo vinyl ketones could be used (entry 20) and only when no steric hindrance impeded the coupling reaction (entry 23). In the presence of 3% $Pd(PPh_3)_4$ the coupling reaction occured readily and in high yield (Table IV). The stereoisomeric purity is again >99% and acid mediated isomerisation provided cleanly the E,E isomer for synthetic and comparative purposes.

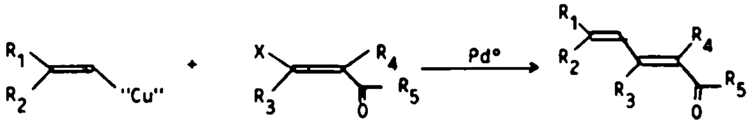


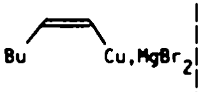
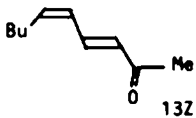
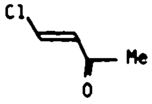
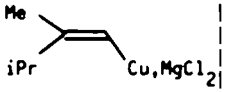
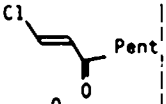
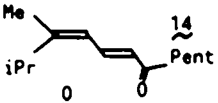
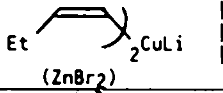
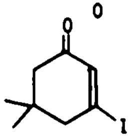
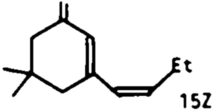
13 E,Z 13 E,E

100 %

With the very hindered ketone shown in entry 23 it was necessary to carry out the reaction with the iodide instead of the chloride, which, even under Pd° catalysis, afforded only 65% yield of the dienone 15. Here again the olfactive properties of the Z isomer were much greater than that of the E isomer (obtained by acidic isomerisation).

Table IV -



Entry	Organocopper reagent	halogeno ketone	Product	Isolated yield
20		 a	 13Z,E	70 %
21	"		" 13Z,E	84 %
22			 14	89 %
23		 b,c	 15Z	90 %

a : without catalyst
b : 15% yield without catalyst
c : 65% yield with the corresponding chloride, under Pd° catalysis

It is clear from the above results, that the Pd° catalyzed acylation of alkenyl copper reagents, is a method of choice for the efficient generation of α,β ethylenic ketones with a known substitution pattern. This synthetic operation is carried out with nearly sotechiometric amount of reagents (1.1 to 1.2 eq. of organometallic reagent), in a one pot procedure, which takes 2-5h for the whole process. The extension of the method to the synthesis of unsymmetrical divinyl ketones and to conjugated dienones shows its wide applicability, especially to Z-ethylenic ketones and dienones which were already known for the higher quality of their olfactive properties.

EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a Jeol MH100 apparatus (CCl_4 ; δ ppm from TMS), ^{13}C NMR on a Jeol FX90 Q ($CDCl_3$; δ ppm). IR spectra were obtained on a Perkin-Elmer model 457 spectrometer. GLPC analyses were performed on a Carlo Erba chromatograph model G 1 and 2150 using a 3m glass column (10% SE 30 or 10% LAC 850 on silanized chromosorb G 80/100 mesh) and 25m capillary glass column (OV 101). The gas chromatograph was coupled to an integrator LTT 9400. All reactions are performed under a nitrogen atmosphere in a 250 ml flask equipped with a low-temperature thermometer, a mechanical stirrer and a pressure equalized addition funnel.

Alkenyl copper and cuprate reagents are prepared according known procedures[6,29]. Ethylenic acids of E configuration are prepared according to ref. 30 ; those of Z configuration according to ref.23. Acid chlorides are either commercially available orprepared according to ref.24, using thionyl chloride in benzene and a catalytic amount ofdimethylformamide.

Mixed carboxylic-carbonic anhydrides are prepared as described in ref.25. β-halogenovinyl ketones are prepared according to ref.27. $Pd(PPh_3)_4$ is commercially available ; we usually prepared it according to ref.31.

Procedure without Pd° catalyst

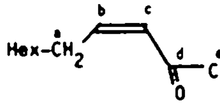
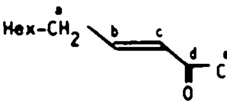
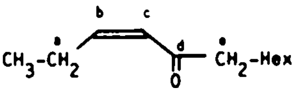
A solution of 30mmol of Z-dinonenyl lithium cuprate is prepared in 100ml Et_2O from n-heptyl lithium (60mmol), copper iodide (33mmol) and acetylene (66mmol). Hexamethyl phosphoric triamide (36g, 200mmol) and 40ml tetrahedropyran are added to this cuprate solution, at -50° and this solution is cooled to -100°. A solution of acetyl bromide (6.15g, 50mmol) in 15ml Et_2O is slowly added and the stirred mixture is allowed to reach room temperature (1h). A yellow precipitate appears during this time. The whole mixture is hydrolyzed, at -10°, with 50ml aqueous ammonium chloride and 10ml aqueous ammonia. The salts are filtered off, the organic phase washed once with 50ml aqueous ammonium chloride, then dried over sodium sulfate. The solvents are removed in vacuo and the residue distilled through a 10cm Vigreux column.

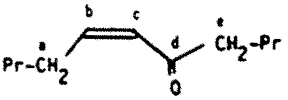
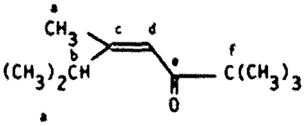
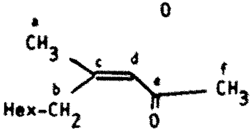
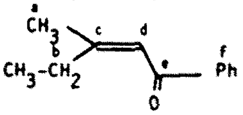
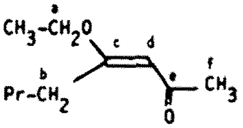
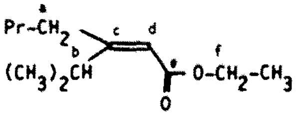
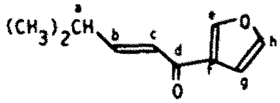
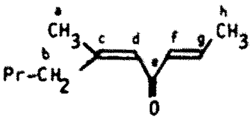
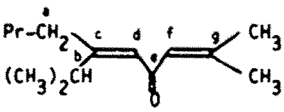
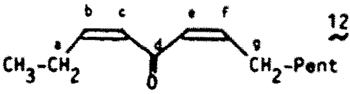
General procedure with Pd° catalyst

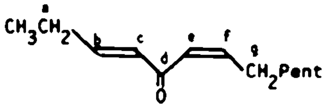
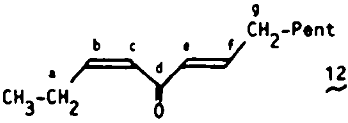
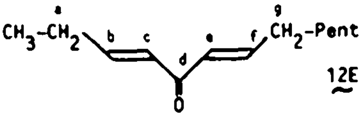
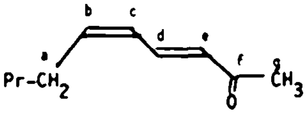
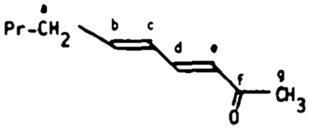
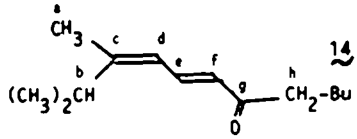
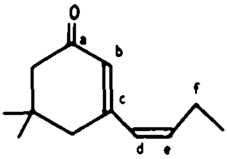
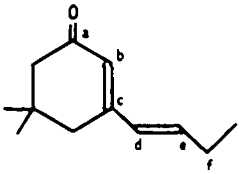
A solution of 30mmol of alkenyl copper reagent (associated with magnesium salts) is prepared in 100ml THF or Et_2O. In the latter case, 60ml of THF are added at -30°. The acid chloride, or the acid anhydride, or the β-halogeno vinyl ketone (25mmol) is mixed with $Pd(PPh_3)_4$ (0.75mmol) in 40ml THF and the whole solution added to the alkenyl copper reagent. The reaction mixture is warmed gradually to room temperature (1h) and, then, hydrolyzed, at -10°, with 50ml aqueous ammonium chloride and 10ml aqueous ammonia. The salts are filtered off and the aqueous phase washed once with 50ml aqueous ammonium chloride. The solvents are removed in vacuo and the residue dissolved in 100ml pentane to precipitate the residual salts. This organic solution is dried over sodium sulfate, concentrated in vacuo and the product distilled.

For lithium dialkenyl cuprate reagents the following procedure is used. To an ethereal solution of 30mmol of cuprate are added 50ml THF and a solution of $ZnBr_2$ (30mmol) in 30ml THF, at -25°C. After 30mn the acid chloride (25mmol) and the $Pd(P(Ph_3)_4$ catalyst (0.75mmol) in THF are added, and the mixture warmed slowly to room temperature (1h). The remaining of the procedure is the same as above.

PHYSICAL AND SPECTROSCOPIC DATA OF THE OBTAINED KETONES

Product		Bp°C mmHg	n_D^{20}	I.R. cm^{-1}	^{1}H RMN (CCl_4, ppm)	^{13}C RMN ($CDCl_3$, ppm)
	1Z	49°/0^{-2}	1.4371	3020 1700 1630 980 725	5.92-6.24(m,2H,Hb and Hc);2.64(dt, 2H,Ha);2.10(s,3H, He)	198.8(d) 148.5(b) 127.0(c)
	1E	a	a	3020 1705 1635 980	6.60(dt,1H,Hb) 5.92(d,1H,Hc) 2.12(s,3H,He) 2.10(dt,2H,Ha) J_{Hb-Hc}=15Hz	198.6(d) 148.6(b) 131.3(c)
	2	75°/5.10^{-2}	1.4439	3020 1695 1620 720	5.96-6.34(m,2H,Hb and Hc);2.57(dq, 2H,Ha);2.18(t,2H, He)	201.6(d) 149.7(b) 126.3(c)

	3	55°/10^{-2}	1.4572	3020 1695 1620 730	5.96-6.32(m,2H,Hb and Hc);2.84(dt, 2H,Ha);2.60(t,2H, Hc)	201.4(d) 148.2(b) 126.8(c)
	4	32°/10^{-2}	1.4509	3020 1680 1610 850	6.34(s,1H,Hd); 3.84(dq,1H,Hb); 1.85(s,3H,Ha)	206.0(e) 163.3(c) 119.5(d) 43.7(f)
	5	82°/5.10^{-2}	1.4443	3020 1690 1615	6.12(s,1H,Hd); 2.56(t,2H,Hb); 2.14(s,3H,Hf); 1.87(s,3H,Ha)	197.7(e) 159.4c) 124.0(d)
	6	101°/10^{-1}	1.5358	3040 1720 1660 1615 1580 855	7.4-8.2(m,5H,Hf); 6.76(s,1H,Hd); 2.68(q,2H,Hb); 1.98(s,3H,Ha)	190.8(e) 161.9(c) 139.3, 132.2, 128.4, 128.2(f) 120.6(d)
	7	47°/10^{-2}	1.4589	2990 1680 1585 960 800	5.46(s,1H,Hd); 3.88(q,2H,Ha); 2.74(t,2H,Hb) 2.06(s,3H,Hf)	196.3(e) 176.0(c) 99.1(d) 63.7(a)
	8	76°/10^{-2}	1.4499	3000 1715 1705 1640 860	5.66(s,1H,Hd) 4.16(q,2H,Hf) 4.08(dq,1H,Hb) 2.18(t,2H,Ha)	169.0(e) 166.5(c) 114.1(d) 59.3(f)
	9Z	52°/10^{-2}	1.5036	3130 3010 1660 1610 910 870 860	8.07(s,1H,He) 7.48(s,1H,Hb) 6.84(s,1H,Hg) 6.45(d,1H,Hc) 6.05(dd,1H,Hb) 3.67(m,1H,Ha) J_{Hb-Hc}=10Hz	185.5(d) 156.2(b) 146.9(e) 144.1(h) 129.3(f) 122.5(c) 108.9(g) 28.3(a)
	9E	58°/10^{-2}	1.5058	3120 3020 1655 1650 1620 980 870	8.21(s,1H,He) 7.56(s,1H,Hk) 7.20(dd,1H,Hb) 6.90(s,1H,Hg) 6.62(d,1H,Hc) 2.56(m,1H,Ha) J_{Hb-Hc}=16Hz	188,7(d) 158.4(b) 149.3(e) 145.0(h) 127.5(f) 123.8(c) 108.1(g) 31.8(a)
	10	58°/10^{-2}	1.4837	3030 1680 1660 1635 1610 970 865	6.90(dq,1H,Hg) 6.24(s,1H,Hd) 6.20(d,1H,Hf) 2.62(t,2H,Hb) 1.92(s,3H,Ha) 1.92(s,3H,Ha) J_{Hf-Hg}=15Hz	189.7(e) 159.8(c) 141.3(g) 133.7(f) 122.9(d)
	11	64°/10^{-2}	1.4668	3020 1675 1660 1620 870 850 785	6.18(s,1H,Hd) 5.82(s,1H,Hf) 4.10(m,1H,Hb) 2.18(t,2H,Ha)	191.6(e) 166.7(c) 153.9(g) 126.5(f) 124.5(d)
	12Z,Z	78°/10^{-2}	i	3010 1675 1660 1620 835 745	5.96-6.44(m,4H, Hb,c,e,f) 2.72(m,4H,Ha and Hg)	192.2(d) 150.0(b) 148.9(f) 128.4(c) 128.0(e)

	12E,Z	85°/10^{-2} 10^{-2}	i	3020 1680 1665 1635 1615 975 740	6.98(dt,1H,Hb) 6.38(d,1H,Hc) 6.24(m,2H,He and Hf) 2.62(m,2H,Hg) 2.26(m,2H,Ha) J_{Hb-Hc}=16Hz	191.3(d) 148.8(b) 148.6(f) 130.9(e) 125.7(b)
	12Z,E	86°/10^{-2}	i	3020 1680 1660 1610 975 745	6.96(dt,1H,Hb) 6.36(d,1H,Hc) 6.24(m,2H,Hb and Hc) 2.68(dd,2H, Ha) 2.22(dt,2H,Hg) J_{He-Hf}=16Hz	191.3(d) 149.8(b) 147.7(f) 131.7(c) 125.3(e)
	12E,E	i	i	3020 1680 1665 1630 980	7.04(m,2H,Hb and Hf) 6.40(d,2H,Hc and He) 2.32(m, 4H,Ha and Hg)	189.6(d) 149.0(b) 147.8(f) 128.7(e) 127.8(b)
	13Z	ii	1.5040	3000 1665 1625 1595 990 955 850	7.53(dd,1H,Hd) 6.16(dd,1H,Hc) 6.14(d,2H,Hc) 5.92(dt,1H,Hb) 2.30(m,2H,Ha) 2.28(s,3H,Hg) J_{Hd-He}=16Hz J_{Hb-Hc}=10Hz	198.4(f) 142.6(d) 137.9(b) 130.3(c) 127.0(e)
	13E	i	i	3020 1680 1660 1590 970 900	7.24(dd,1H,Hd) 6.25(m,3H,Hb,c,e) 2.28(s,3H,Hg) 2.24(m,2H,Ha)	198.9(f) 145.8(d) 144.2(b) 128.9(c) 128.7(e)
	14	116°/10^{-2}	1.5037	3030 1680 1655 1620 1580 970 880	7.56(dd,1H,He) 6.08(d,1H,Hf) 5.91(d,1H,H,Hd) 3.19(m,1H,Hb) 2.53(t,2H,Hb) 1.78(s,3H,Ha) J_{He-Hf}=15Hz J_{Hd-He}=12Hz	200.9(g) 156.2(c) 137.3(e) 127.5(f) 123.4(d)
	15Z	78°/10^{-2}	1.5117	3000 1660 1630 900 875 855	6.02(s,1H,Hb) 5.84(d,1H,Hd) 5.72(dt,1H,He) 2.36(m,2H,Hf) J_{Hd-He}=12Hz)	199.7(a) 155.9(c) 139.9(e) 128.5(d) 126.3(b)
	15E	ii	1.5262	3020 1660 1630 1590 970 900 880 855	6.30(m,2H,Hd and He) 5.96(s,1H,Hb) 2.24(m,2H,Hf)	200.5(a) 156.0(c) 140.6(e) 130.5(d) 124.9(b)

i : crude product
ii: isolated by column chromatography

ACKNOWLEDGEMENTS

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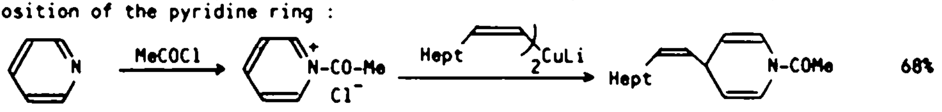
10. At low temperature (-100°C) hexamethyl phosphoric triamide is partly insoluble in diethyl ether and tetrahydrofuran (one quarter of the total volume) is used as homogenizing cosolvent.
11. In the presence of pyridine the reaction proceeded by attack of the cuprate to the 4 position of the pyridine ring :



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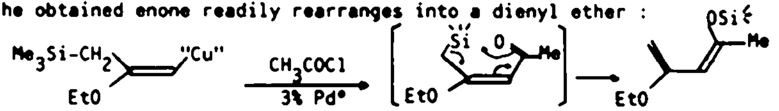

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