STEREOSELECTIVE ADDITION OF ORGANOCUPRATES TO A CHIRAL α-β ETHYLENIC OXAZOLIDINE: MECHANISM, NATURE AND REACTIVITY OF THE INTERMEDIATES

J. BERLAN*, Y. BESACE, G. POURCELOT and P. CRESSON

Laboratoire de Synthèse organique, Ecole Nationale Supérieure de Chimie de Paris, 11 Rue Pierre et Marie Curie, 75231 Paris Cedex 05 (France)

(Received May 23rd, 1983)

Summary

The reaction of organocuprates with the oxazolidine derived from (E)-cinnamaldehyde and ($-$)-ephedrine gives initially two organocopper intermediates. The steric course of the reaction and spectroscopic data clearly indicate a slow equilibrium between these two highly stable, low reactivity, intermediates. Although an S'_N2 mechanism cannot be totally excluded, an unusual 1,2-addition of the organocuprate to the carbon–carbon double bond of the unsaturated oxazolidine better accounts for the steric course of the reaction.

The diastereoselective addition of organocopper reagents to chiral α,β-unsaturated oxazolidines has recently been described [1]. In connection with attempts to improve the optical yield [2,3] we have investigated the mechanism of the reaction, in particular with respect to the determination of the nature and the reactivity of the intermediate(s). For this purpose the model oxazolidine (1) obtained from cinnamaldehyde and ($-$)-ephedrine was treated with methylcopper-lithium iodide (Z = I) (2), represented as CH_3CuI,Li [4] or lithium dimethylcuprate (Z = CH_3), (2') according to Scheme 1.
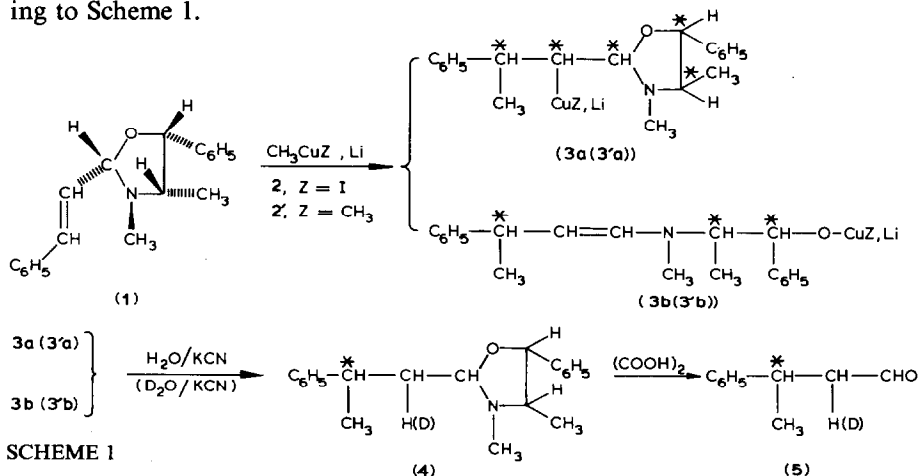
SCHEME 1

After mild hydrolysis the saturated oxazolidine (4), is obtained, and this on treatment with oxalic acid gives optically active 3-phenyl butanal (5) in almost quantitative yield [5]. Hydrolysis with deuterium oxide gives the parent deuteriated compounds, well characterized by their NMR and mass spectra [1a]. Two mechanisms could account for the formation of 4:

(a) An $S'_N 2$ displacement giving the alkoxycopper derivative 3b, followed by a fast ring closure after hydrolysis during the work up.

(b) A 1,2-addition of the organocopper reagent, leading to the intermediate organocuprate 3a.

However, dissociation of these organocopper species could not be a priori excluded.

We now describe our first studies of the nature of the intermediates, which suggest that the first step of the reaction in hexane, and most probably in ether, is a 1,2-addition to the carbon–carbon double bond, and that is followed by a 3a ⇌ 3b (or 3'a ⇌ 3'b) equilibrium.

I. Nature and reactivity of the intermediates

(a) The intermediates from the reactions in Scheme 1 are organocopper derivatives

This is clearly established by the dissolution of these insoluble species in ether following addition of copper complexing agents such as trimethylphosphite or tributylphosphine.

When an ethereal solution of 1 is added to a suspension of two equivalents of the heterocuprate 2 in ether no reaction occurs and a yellow solid is present throughout the run. The reaction is complete within 3 h at 5°C [6] but hydrolysis of the supernatant solution gives 4 in less than 10% yield. Addition of one equivalent of trimethylphosphite per mole of copper results in partial dissolution and subsequent hydrolysis of the supernatant solution gives 4 in quantitative yield. Thus the precipitate present is the molar excess of 2, which can be detected by its NMR signal (-0.9 ppm in ether at 25°C) after its solubilisation by further addition of trimethylphosphite or by its reaction in situ, after separation of the supernatant solution, with one equivalent of methyl 3-phenylpropiolate, which gives a quantitative yield of a mixture of (E/Z)-3-phenyl butenoates. This is illustrated in Scheme 2.
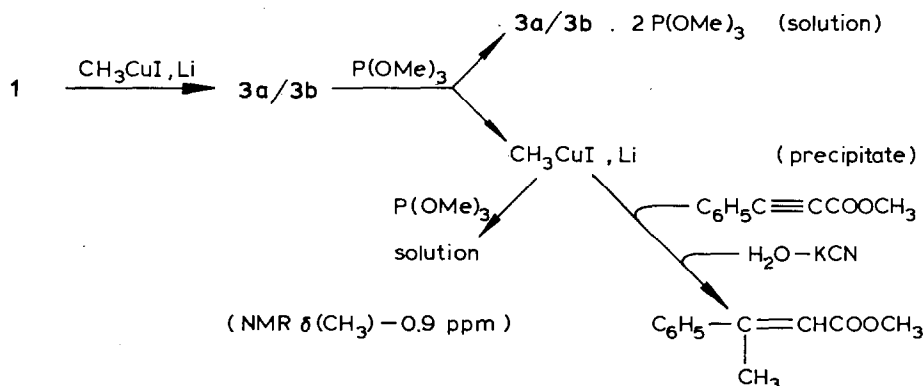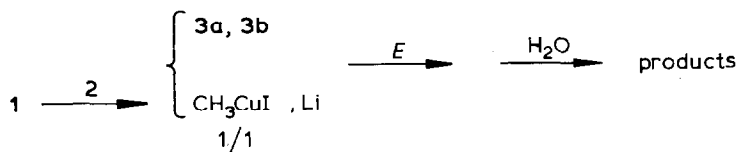

SCHEME 2

The same occurs when triphenyl- or tributyl-phosphine is used in place of trimethylphosphite.

Thus it is possible to separate the intermediates 3 from the excess of hetero-cuprate 2 by selective solubilisation with phosphines or phosphites.
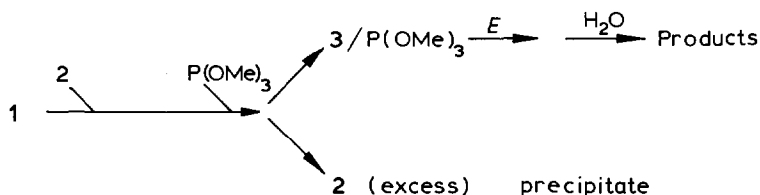
Similarly the partially soluble intermediates resulting from the addition of one equivalent of lithium cuprate 2′ to 1 are completely soluble in the presence of phosphines or phosphites.

(b) Reactivity of the intermediates

Several electrophiles *E* were added to the reaction mixture either directly in situ (Scheme 3a) or after separation of the intermediates 3 by selective dissolution (Scheme 3b).

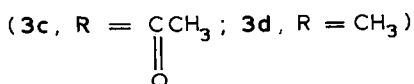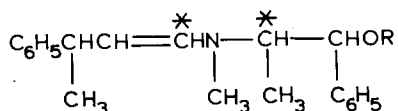$$1 \xrightarrow{2} \begin{cases} 3a, 3b \\ CH_3CuI, Li \\ 1/1 \end{cases} \xrightarrow{E} \xrightarrow{H_2O} products$$

SCHEME 3a

$$1 \xrightarrow{2 \quad P(OMe)_3} \begin{cases} 3/P(OMe)_3 \xrightarrow{E} \xrightarrow{H_2O} Products \\ 2 \text{ (excess)} \quad precipitate \end{cases}$$

SCHEME 3b

In both types of experiments, in ether the intermediates 3 failed to react with benzylidene acetone [7], methyl 3-phenylpropiolate [7], methyl iodide, or benzyl bromide. Upon hydrolysis only the oxazolidine 4 was obtained, in quantitative yield. With acetyl chloride 3c was obtained in almost quantitative yield within a few hours. The same type of product 3d was obtained with methyl iodide within 12 h at room temperature in a $Et_2O/HMPA$ (1/1) mixture.

$$\underset{\underset{CH_3}{|}}{C_6H_5CHCH}=\overset{*}{C}HN-\overset{*}{\underset{\underset{CH_3}{|}}{C}H}-\underset{\underset{C_6H_5}{|}}{C}HOR$$

$$(3c, R = \underset{\underset{O}{\|}}{C}CH_3; \ 3d, R = CH_3)$$

Saponification of 3c resulted in quantitative formation of 4. However the formation of compounds 3c and 3d does not necessarily imply that 3b is the sole intermediate. This is clearly demonstrated by the following spectroscopic studies.

## II. Identification of the intermediates by IR and NMR spectroscopies

A clean stable solution of the intermediates **3** in CD_2Cl_2 can easily be obtained (vide experimental part). The IR spectrum exhibits an intense sharp characteristic absorption band at 1650 cm^{-1}, which can be unambiguously assigned to the enamine system of the intermediate **3b**. From the NMR spectrum (250 MHz) several observations can be made. First the presence of two equivalents of trimethyl phosphite (doublet; 3.74 ppm) is confirmed and the presence of three equivalents of residual Et_2O is established. In addition to the complex systems, between 1–5 ppm, there are two other groups of relatively broad signals, and these can be analyzed, namely a doublet (J 7 Hz) centered at 0.9 ppm and two hardly resolved doublets (J 7 Hz) at 0.60 and 0.56 ppm. Together these two sets of signals account for three protons, and must be respectively assigned to the methyl group A of the ephedrine moiety of **3b** and **3a** [8]. This assignment is based because of the shielding effect of the adjacent phenyl ring, the methyl group A of the ephedrine system resonates at higher field ($\Delta\delta \cong 0.3$) in the rigid cyclic compounds (**3a**, **1**, **4** etc.) than in acyclic derivatives such as **3b**, **6**, **7** as illustrated.
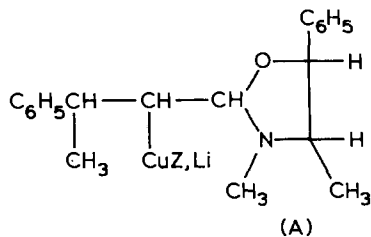
$(\delta \simeq 0.6, 0.56 \text{ ppm}, J \text{ 7 Hz})$

$(\textbf{3a}, Z = I \; ; \; \textbf{3'a}, Z = CH_3)$
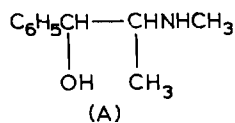
$(\delta \text{ 0.9 ppm})$

$(\textbf{6})$
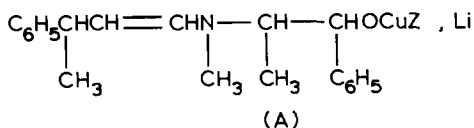
$(0.9 \text{ ppm}, J \text{ 7 Hz})$

$(\textbf{3b}, Z = I \; ; \; \textbf{3'b}, Z = CH_3)$
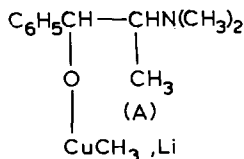
$(\textbf{7})(\delta \text{ 0.88 ppm})$
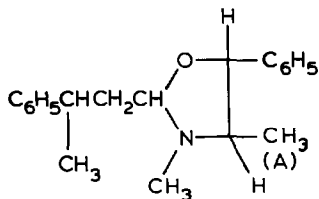
$(\delta, 0.58, 0.53 \text{ ppm} \; ; \; J \text{ 7 Hz})$

$(\textbf{4})$

These results are consistent with a slow equilibrium between the two intermediates **3a**, **3b** (**3a**/**3b** 40/60). A similar equilibrium **3'a** $\rightleftharpoons$ **3'b**, based on identical observations occurs after the addition of one equivalent of lithium dimethylcuprate

2′ to 1. In this case complete solubilisation of the intermediates needs 3 equivalents of trimethylphosphite, and a new singlet appears at − 1 ppm which can be assigned to the methyl copper group Z of 3′a (3′a/3′b 25/75) [9]. However the observation of these equilibria, 3a ⇌ 3b or 3′a ⇌ 3′b does not answer the question of the actual mechanism of the reaction. This can be done in the following way.
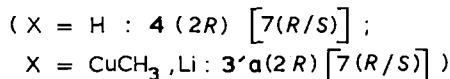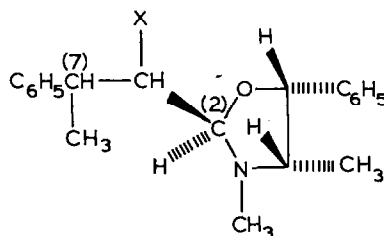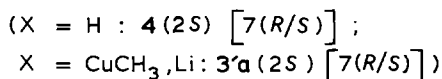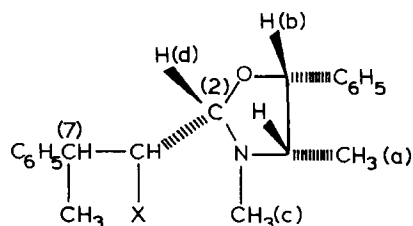
III. Mechanism of the reaction

(a) NMR study of the resulting oxazolidines 4

We recently reported [1a] that the α,β-ethylenic oxazolidine (1) is a thermodynamic mixture of the two $(2S)/(2R)$ epimers, at carbon C(2) in a 93/7 ratio.

After the reaction of 1 with lithium dimethylcuprate both the cyclic intermediate 3′a and the saturated oxazolidine (4) exhibit R/S isomerism at asymmetric carbons C(2) and C(7). Four $2(R/S)/7(R/S)$ isomers can thus be expected. (The situation is even more complex for 3′a owing to the asymmetry at carbon C(6). However this problem is not of crucial importance for the following discussion and will not be considered here).

$(X = H : 4 (2S) \left[7(R/S) \right]$;
$X = CuCH_3 , Li : 3'a (2S) \left[7(R/S) \right]$)

$(X = H : 4 (2R) \left[7(R/S) \right]$;
$X = CuCH_3 , Li : 3'a(2R) \left[7(R/S) \right]$)

The four isomers of 4 were identified by NMR spectroscopy (100 MHz) as depicted in Table 1.

The $7(R/S)$ ratio, which allows accurate determination of the optical purity of 3-phenyl butanal 5 from NMR spectra of crude 4, is definitely fixed in the early stage of the reaction (methyl transfer from the cuprate to the substrate) since no equilibrium at carbon C(7) can be detected. For a given substrate it depends on the nature of the cuprate [2], of the solvent [3] and on temperature [3] but is independent of reaction time and hydrolysis conditions and will not be discussed further.

TABLE 1

NMR SPECTROSCOPIC CHARACTERISTICS OF COMPOUND 4 (δ,ppm)

	7(R) 2(S)	7(R) 2(R)	7(S) 2(S)	7(S) 2(R)
a	0.53	0.53	0.58	0.44
b	4.8	5.12	4.86	5.12
c	2.0	2.24	2.12	2.20
d	3.44	4.5	3.86	4.12

TABLE 2

INFLUENCE OF REACTION CONDITIONS ON 4(2S)/4(2R) RATIO

Entry	Solvent	Time	Temperature	Hydrolysis conditions	2S(%)	2R(%)
1	Ether	2 h	−42°C	H_2O/KCN	93	7
2	Ether	2 h	−42°C	reaction mixture poured into hexane H_2O/KCN mixture with vigorous stirring	65	35
3	Hexane	6 h	−42°C	H_2O/KCN, −42°C fast warming up to R.T. with vigorous stirring	93	7 [a]
4	Hexane	6 h then 30 h	−42°C R.T.	H_2O/KCN, R.T.	70	30 [a]
5	Hexane	6 h then 72 or 96 h	−42°C R.T.	H_2O/KCN, R.T.	45	55
6	Hexane	10 min	R.T.	H_2O/KCN, R.T.	65	35
7	Hexane	1 h	R.T.	H_2O/KCN, R.T.	50	50
8	Hexane	10 min	R.T.	Fast cooling at −42°C, hydrolysis at −42°C	65	35 [a]
9	Hexane	10 min then 12 h 24 h 24 h	R.T. at 0°C at −20°C at −42°C	H_2O/KCN, −42°C fast warming up to R.T. with stirring	65	35

[a] Supernatant solution and precipitate were separated with the following results. Yields are calculated for isolated 4 based on 1.

Entry	Supernatant		precipitate	
	4 (%)	(2S)/(2R)	4 (%)	(2S)/(2R)
3	10	90/10	90	93/ 7
4	40	60/40	60	80/20
8	10	65/35	90	65/35

On the other hand the 2(R/S) ratio strongly depends on the reaction conditions and especially on these two latter parameters. In order to determine why different 4(2R)/4(2S) ratios were obtained, both the addition of lithium dimethylcuprate and the hydrolysis were carried out under strictly controlled conditions. The results are shown in Table 2.

In the first place these results afford new evidence for a 3′b ⇌ 3′a equilibrium in the reaction mixture: if 3′b were the sole intermediate, identical 4(2R)/4(2S) ratios would be obtained under the same hydrolysis conditions. Obviously this is not the case (compare entries 1, 2; 4, 5, 6). Thus formation of different 4(2S)/4(2R) mixtures can only be explained in terms of 3′a(2S) ⇌ 3′b ⇌ 3′a(2R) equilibria. Upon hydrolysis 3′a(2S) should lead to 4(2S) and 3′a(2R) to 4(2R), but unfortunately no such forecast can be made for 3′b. Moreover the problem is complicated by the observation that any ethereal solution of 4(2S)/4(2R) derivatives, in a ratio different from 93/7, is readily equilibrated to a 93/7 mixture upon stirring within: (i) a few seconds with aqueous acidic solution; (ii) less than two minutes with water

or the aqueous layer resulting from the hydrolysis of the reaction (Scheme 1); and (iii), less than 1.5 h with basic aqueous potassium cyanide.

Equilibration is about 20 times slower, under the same conditions, with hexane solutions of 4(2S)/4(2R) mixtures [10]. This clearly indicates that at thermodynamic equilibrium 4, like 1, is obtained as a (2S)/(2R) 93/7 mixture. This is also the case when 4 is prepared under the same conditions as 1 from 3-phenylbutanal (5) and (−)-ephedrine, whatever the enantiomeric purity of 5.

Thus equilibration during hydrolysis accounts for the fact that in ether 93/7 4(2S)/4(2R) mixtures are always obtained, (see for instance, Table 2 entry 1). Different 4(2S)/4(2R) ratios can only be obtained in hexane (entries 3–9) or when the ethereal reaction mixture is poured with stirring in an hexane aqueous KCN mixture (Table 2, entry 2). Under these conditions hydrolysis is complete within 2–4 min and is much faster than epimerization at carbon C(2). Reproducibility is fairly good (4(2R/2S) ratios vary within a ±5% range) and the results reported in Table 2, which are average values for at least four identical runs, can be assumed to give an accurate picture of the composition of the intermediate 3′b, 3′a (2R/2S) mixture prior to hydrolysis. In order to gain further insight on this intermediate mixture, an IR spectrometric study was carried out.

*(b) Infrared study of the reaction mixture*

In ether the reaction is complete within less than 2 h at −42°C and the medium is almost homogeneous. At 0.05 M concentration the strong absorption band at 1650 cm^{-1} corresponding to 3′b is observed.

In hexane at −42°C the reaction mixture is markedly heterogeneous as the precipitate contains more than 90% of the overall material (see Table 2, entry 3). The reaction is complete within about 6 h, the precipitate shows no band at 1650 cm^{-1}, indicating that under these conditions the intermediates are almost exclusively the insoluble 3′a(2R)/3′a(2S) species. At higher temperature partial solubilisation occurs (Table 2, entry 4), and at 0.05 M concentration the 1650 cm^{-1} band assigned to 3′b is observed. This absorption band is about 3 times as strong in ether as in hexane under identical conditions of temperature and concentration.

(c) Discussion of the mechanism of the reaction

As already noted two mechanisms can be suggested:
(a) An $S'_N 2$ process:

$$1(2S) \xrightarrow{2'} 3'b \begin{cases} \nearrow 3'a(2S) \\ \searrow 3'a(2R) \end{cases} \left. \right\} \xrightarrow[KCN]{H_2O} 4$$
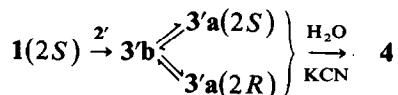
SCHEME 4

(b) A 1,2-addition to the carbon–carbon double bond of 1, followed by equilibration via the "open" intermediate 3′b according to Scheme 5:

$$1(2S) \xrightarrow{2'} \underbrace{3'a(2S) \rightleftharpoons 3'b \rightleftharpoons 3'a(2R)}_{\qquad \rightarrow 4}$$
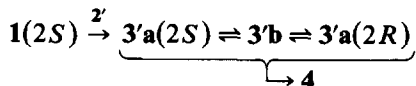
SCHEME 5

(In Schemes 4 and 5 only the major (2S) isomer of **1** is shown).

When the reaction is carried out in ether and hydrolysed in hexane (Table 2, entry 2) a 65/35 **4**(2S)/**4**(2R) mixture is obtained. As the reaction time has no influence, within experimental error, on this **4**(2S)/**4**(2R) ratio, it must be assumed that **3′b**, **3′a** (2S/2R) equilibria are rapidly established and that the thermodynamic state of the system is established virtually immediately.

In contrast, when the reaction is carried out in hexane striking differences, depending on time and temperature, are observed (compare Table 2 entries 3, 4, 5 and 6, 7, 8). At −42°C a 93/7 **4**(2S)/**4**(2R) mixture is obtained (entry 3) corresponding to thermodynamic ratios of both oxazolidines **4** and **1** (vide supra). The precipitate and supernatant solution are nearly identical within experimental error. This is no longer the case when the reaction mixture is kept at room temperature (entry 4), and equilibrium is reached within 72 h (entry 5) leading to a 45/55 **4**(2S)/**4**(2R) mixture. Owing to the heterogeneity of the reaction medium it is necessary to consider not only the **3′b**, **3′a**(2R/2S) equilibria in solution but also exchange between the precipitate and supernatant solution. This probably accounts for the very low rate of equilibration.

If the reaction proceeds via an S'_N2 mechanism according to Scheme 4, quantitative formation of **3′b** at −42°C, which could lead to a 93/7 **4**(2S)/**4**(2R) mixture upon hydrolysis, can be wholly excluded in the light of the results of the IR study (vide supra). It would thus have to be assumed that formation of **3′b** is followed by a fast kinetically-controlled ring closure to give a 93/7 **3′a**(2S)/**3′a**(2R) mixture. (Upon hydrolysis an identical **4**(2S)/**4**(2R) ratio would be obtained.) Although this cannot be totally excluded such a coïncidence seems unlikely.

A 1,2-addition, according to Scheme 5, followed by slow establishment of **3′a**(2S) ⇌ **3′b** ⇌ **3′a**(2R) equilibria, better accounts for the reported results: the 93/7 **1**(2S)/**1**(2R) mixture leads, on reaction with lithium dimethylcuprate **2′**, to the same **3′a**(2S)/**3′a**(2R) ratio. At −42°C equilibration is very slow, and upon hydrolysis a 93/7 **4**(2S)/**4**(2R) mixture is obtained. Then, on standing at room temperature equilibration occurs via the "open" **3′b** intermediate. When the reaction is carried out at room temperature equilibration is much faster, although still slower than addition itself (compare entries 6,7), probably due to much higher solubilities of the intermediates, but the results are also consistent with the 1,2-addition reaction pathway.

Finally it should be noticed that the hydrolysis temperature itself has little if any, influence, on the **4**(2S)/**4**(2R) ratio (entries 8,9). Similar observations can be made for addition of lithium diphenylcuprate to the oxazolidine derived from crotonaldehyde and (−)-ephedrine. The same **3′a**, **3′b** intermediates are obtained, but the overall results do not correspond exactly because the enantiomeric excesses are not the same [2].

In conclusion, although a S'_N2 reaction mechanism cannot be totally excluded it seems to us that a 1,2-addition to the carbon–carbon double bond of the unsaturated oxazolidine better accounts for the reported results. To our knowledge the demonstrated equilibrium **3a**(**3′a**) ⇌ **3b**(**3′b**) is the first example of this kind of behaviour in organocopper chemistry.

These results can be related to the 3,4-addition mechanism of cuprates to α-allenic [11] or acetylenic [12] carbonyl compounds. In both cases a subsequent α-cuprio-ketone(or ester)-copper enolate equilibrium has been established. There is

evidence for similar phenomena in the case of α,β-ethylenic ketones [13].

Investigations are in progress on other oxazolidine systems, in order to obtain information about the mechanism of the reaction.

Experimental

Infrared spectra were recorded on a Perkin–Elmer 237 spectrophotometer, and NMR spectra on a Varian XL 100 or Cameca 250 spectrometer (TMS as internal standard). Mass spectra were recorded on a Ribermag R 10-10 C mass spectrometer.

All reactions involving organocopper compounds were performed under argon in two-neck round bottom flasks charged with copper iodide and equipped with rubber septums. Before the introduction of solvent or reagents, the apparatus was dried with a Bunsen burner flame while being evacuated and then filled with argon.

Solvents and reagents solutions were introduced via hypodermic syringes.

IR spectra of organocopper intermediates were recorded using sealed NaCl cells (1 mm) purged with argon and filled under an argon atmosphere. The NMR spectra of the organocopper were obtained using sealed NMR tubes, purged with argon and filled with hypodermic syringes through rubber septums; solutions, 0.5 M in dichloromethane-d_2, were obtained as follows. The ethereal suspension or solution of the organocopper species was evaporated under vacuum (30 min; 10^{-2} torr), and to the solid residue was added two equivalents of trimethylphosphite in the appropriate volume of dichloromethane-d_2 at 0°C. The clear solution was carefully filtered and transferred to the NMR tube.

Reagents and solvents

Commercial copper iodide (Prolabo) was found to be satisfactory in comparisons with samples purified by standard procedures [15].

Methyllithium (Alfa inorganics) was standardized as described in ref. 16. Trimethyl phosphite (Janssen) was carefully distilled under argon and stored under argon over 4Å molecular sieve.

HMPA was distilled from calcium hydride and stored under argon over 4Å molecular sieve.

Ether was freshly distilled from lithium aluminium hydride under argon.

Electrophiles: acetyl chloride, methyl iodide, benzyl bromide, and benzalacetone (Aldrich) were freshly distilled. Phenyl propiolate was prepared from phenyl propiolic acid (Aldrich) and one equivalent of diazomethane and used without further purification.

(−)-Ephedrine (Prolabo) was used without further purification. The (−)-N-methylephedrine was generated from its chlorohydrate (Aldrich) and dried by azeotropic distillation of benzene followed by 24 h under vacuum. Oxazolidine 1 was prepared as described in ref. 1 and solutions of organocuprates in ether were made by the usual procedure (see for example ref. 14).

Selective solubilisation of the organocopper intermediates

To an ethereal suspension of methylcopper-lithium iodide (2) (10^{-2} mol in 10 ml of ether) oxazolidine 1 (5×10^{-3} mol in 30 ml of ether) is added dropwise at − 78°C and mixture is stirred for 3 h at 5°C. Trimethyl phosphite (10^{-2} mol) in 1 ml of ether is added at 5°C, causing partial dissolution of intermediates 3a,3b. Total

dissolution occurs after further addition of trimethyl phosphite (10^{-2} mol in 1 ml of ether).

After partial dissolution the precipitate (CH_3CuI,Li) can be separated. After standing the clear supernatant solution is removed and the precipitate washed twice with 10 ml of ether. The clear ethereal solutions are mixed and concentrated to 20 ml under vacuum at 5°C. Addition of methyl-3-phenyl propiolate (5×10^{-3} mol in 5 ml of ether) at 0°C gives, after hydrolysis, a mixture of (E/Z)-3-phenyl butenoates, as already reported [12].

Triphenylphosphine or tributylphosphine (10^{-2} mol) can be added in place of trimethyl phosphite.
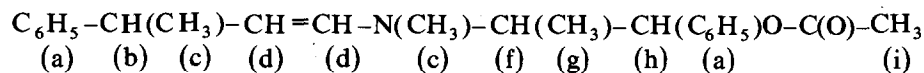
Reactivity of the intermediates

In situ addition of electrophiles according to Scheme 3a. After reaction of **1** (5×10^{-3} mol) with two equivalents of cuprate **2** (10^{-2} mol), an ethereal solution of the electrophile E (9×10^{-3} mol in 5 ml of ether) is added at 0°C. The mixture is stirred overnight at room temperature and quenched with H_2O/KCN. Extraction with ether gives a quantitative yield of the saturated oxazolidine **4**, together with a mixture of the starting electrophile and the product of this electrophile with **2** in the cases when E is benzalacetone, methyl-3-phenyl propiolate or benzyl bromide. (The products were identified by comparison with authentic samples). Oxazolidine **4** is soluble in 4 N hydrochloric acid and can be separated.

Reaction with electrophiles according to Scheme 3b. The intermediates resulting from reaction of **1** with two equivalents of **2** are selectively taken into solution with trimethyl phosphite as described above. The clear ethereal pale yellow solution is concentrated under vacuum and the electrophile (5×10^{-3} mol in 5 ml of ether) is added dropwise at 0°C. The mixture is stirred overnight at room temperature and hydrolysed with H_2O/KCN solution. Extraction with ether gives **4**, together with some recovered electrophile, and **4** is separated by selective dissolution in 4 N HCl.

Reaction with acetyl chloride. An ethereal solution of acetyl chloride (10^{-2} mol) is added to the initial product mixture as in Scheme 3a. The mixture is stirred overnight at room temperature and quenched with aqueous KCN solution. After extraction with ether (2×10 ml) the organic layer is washed with saturated aquous K_2CO_3 and than water. The solution is dried over magnesium sulfate and filtered, and the ether is removed under vacuum. **3c** isolated in 80% yield, is identified from its IR, NMR and mass spectra.

$m/e = 341$. IR: $\nu(CO)$ 1740 cm^{-1}; $\nu(C=C-N)$ 1645 cm^{-1}.
NMR:

$$C_6H_5-CH(CH_3)-CH=CH-N(CH_3)-CH(CH_3)-CH(C_6H_5)O-C(O)-CH_3$$
$$\quad\text{(a)}\quad\text{(b)}\quad\text{(c)}\quad\text{(d)}\quad\text{(d)}\quad\text{(c)}\quad\text{(f)}\quad\text{(g)}\quad\text{(h)}\quad\text{(a)}\qquad\text{(i)}$$

δ(ppm): (a) 7–7.5 m; (b) 3.4 quint, J 7 Hz; (c) 1.2 d, J 7 Hz; (d) 4.15–4 d, J 14 Hz; (e) 2.45 s; (f) 2.7 quint, J 7 Hz; (g) 1.05 d, J 7 Hz; (h) 5.7 d, J 7 Hz; (i) 2.05 s.

Saponification of 3c. A mixture of **3c** (300 mg in 3 ml of ethanol) and potassium hydroxide (100 mg in 5 ml of water) is refluxed for 2 h. 10 ml of water are then added and the mixture is extracted with ether, to give **4** in quantitative yield.

Reaction with methyl iodide. In ether, under the conditions used for acetyl chloride, no reaction is observed. When the methyl iodide is added in 20 ml of

HMPA, **3d** is obtained in almost quantitative yield.

$m/e = 313$. IR $\bar{\nu}$(C=C–N) 1650 cm^{-1}; NMR: protons a–g are identical, within experimental error to the corresponding protons from **3c**, (h) 5.2 d, J 7 Hz; (i) 3.15 s.

Preparation of heterocuprate (7). Compound **7** is prepared by addition of N-methylephedrine (5×10^{-3} mol in 10 ml of ether) to an ethereal solution of lithium dimethylcuprate at 0°C. The resulting yellow-brown precipitate dissolves upon addition of four equivalents of trimethyl phosphite.

Reaction of 1 with lithium dimethylcuprate (2'). (a) In ether: A solution of oxazolidine (**1**) (9×10^{-3} mol in 30 ml of ether) is added dropwise to lithium dimethylcuprate (10^{-2} mol in 10 ml of ether) at -42°C (dry ice/acetonitrile bath). The pale yellow homogeneous mixture is stirred for 2 h (a light yellow precipitate begins to appear after 1.5–2 h). Hydrolysis is carried out by addition of aqueous KCN solution or by pouring the mixture with vigourous stirring into hexane (50 ml) and KCN aqueous solution (10 ml).

(b) In hexane: A suspension of lithium dimethylcuprate (**2'**) in hexane can be prepared from an ethereal solution of **2'** by removing ether under vacuum (10^{-2} torr) at 5°C and adding 10 ml of hexane to the solid light grey residue. However we have found that 3 mol of ether remain per mol of copper [3]. To this light grey suspension of **2'**(10^{-2} mol) 0.9 mol of oxazolidine (**1**) (in 30 ml of hexane) is added at -42°C or at room temperature. Hydrolysis is carried out with aqueous KCN solution.

After extraction with hexane (2×10 ml) the organic layer is dried with magnesium sulfate (10 min) and filtered. Oxazolidine (**4**) is obtained in quantitative yield.

3-Phenylbutanal (**5**) is obtained as described elsewhere [1] and purified by preparative TLC; (Silica Gel Merck, 60F$_{254+366}$ ether/pentane 80/20. Yield of **5** 85%.

Equilibration of 4(2S)/4(2R) mixtures. A 50/50 4(2S)/4(2R) mixture can be made easily and rapidly (Table 2, entry 6) as colorless oil; 500 mg of this mixture in 10 ml of ether (or hexane) are vigorously stirred with 10 ml of either (a) 10^{-1} M *para*-toluenesulfonic acid in water, (b) water, (c) the aqueous solution obtained by hydrolysis of the product mixture from of oxazolidine (**1**) with lithium dimethylcuprate (**2'**), or (d) 10^{-1} M KCN in water. Hexane (40 ml) is then added and the organic layer is separated, washed with 10 ml of water and dried for 10 min over magnesium sulfate (Under these conditions a 50/50 4(2S)/4(2R) mixture is not equilibrated by magnesium sulfate).

References

1 (a) M. Huché, J. Aubouet, G. Pourcelot and J. Berlan, Tetrahedron Lett., 24 (1983) 585; (b) P. Mangeney, A. Alexakis and J.F. Normant, ibid., 24 (1983) 373.
2 J. Berlan, D. Prat, Y. Besace and P. Cresson, to be published.
3 J. Berlan, Y. Besace, M. Huché and P. Cresson, to be published.
4 The actual nature and structure of the organocopper species resulting from the addition of methyllithium to one equivalent of copper iodide are not known. The suggested heterocuprate representation is used to emphasize the difference between this species and methylcopper or a methylcopper/lithium iodide mixture, which do not react with **1** [2].
5 After purification (by distillation or chromatography) **5** is obtained in more than 85% yield.
6 Much lower yields are obtained when the reaction is carried out with only one equivalent of **2**, even for longer reaction times.

7 As indicated in Scheme 3a, the products obtained are those from reaction of excess **2**.

8 The two doublets for the methyl group A in **3a**,**3′a** arise from the two configurations of carbon C(7). Similar behaviour is observed with the saturated oxazolidine (**4**) [2].

9 We could not detect the signal of the copper methyl group Z in **3′b**. The ^{1}H NMR spectrum of compound **7** and the heterocuprate t-$C_4H_9OCuCH_3$,Li dissolved in the same way in CD_2Cl_2 also do not show this signal. Probably the methyl group of cuprates of the type $ROCuCH_3$,Li resonates at lower field and overlaps with the methyl signal of the residual ether.

10 Slow equilibration also occurs in dry CCl_4 (within few hours) and can be followed by NMR spectroscopy. It should also be noted that the $7(S)/7(R)$ ratios are not the same in the two $2(S)/2(R)$ epimers. In methanol-d_4 only the $4(2S)$ isomer is detected by NMR spectroscopy.

11 J. Berlan, J.P. Battioni and K. Koosha, Tetrahedron Lett., (1976) 3355, Bull. Soc. Chim. Fr II, (1979) 183.

12 J. Klein and R. Levene, J. Chem. Soc. Perkin II, (1973) 1971.

13 (a) H. Rivière and P.W. Tang, Bull. Soc. Chim. Fr., (1973) 2455; (b) C.R. Acad. Sci. Paris C, 274 (1972) 1944; (c) P. Four, H. Riviere and P.W. Tang, Tetrahedron Lett., (1977) 3879; (d) G.H. Posner and C.M. Lentz, ibid., (1977) 3215.

14 G.H. Posner, Org. Reactions, 19 (1972) 1.

15 (a) G.B. Kauffman and R.P. Pinnell, Inorg. Synth., 6 (1960) 3; (b) R.N. Keller, H.D. Wycoff, ibid., 2 (1946) 1.

16 A.F. Clifford and R.R. Olsen, Analyt. Chem., 32 (1960) 544.