

UNIVERSITY OF SOUTH AFRICA
STUDIA 11

ORGANOMETALLIC COMPOUNDS:
INTERMEDIATES
IN ORGANIC SYNTHESIS

G. McGillivray

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There is little doubt that today we are living in the electronic age, the age of the instrument, the age of the computer. The impact of all these "machines" is particularly noticed in science, and organic chemistry is no exception. Thus we have a myriad of instruments, often coupled to computers, to assist us in the elucidation of the structures of organic molecules and the solving of other problems of what one might call collectively, an analytical nature.

It is only natural to ask, therefore, "Is there not a danger that one day the organic chemist will be replaced by a machine?". The answer to this is surely, "No", for although we will use machines more and more to assist us, the ingenuity of the human mind is still required for further development, development highly necessary if organic chemistry is to keep abreast with the other branches of science. This is particularly true for developments in organic synthesis as was emphasised by the citation¹ when R. B. Woodward was awarded the Nobel Prize in Chemistry in 1965 for "Contributions to the Art of Chemical Synthesis". I think it is safe to assume that the creative side of art will always remain the prerogative of the living mind and never become that of the machine.

I am assured by my colleagues of the Department of Computer Science that a computer cannot think. As one of the primary objects of a university is surely to teach students to think, then it must be logical to teach them to do what the computer cannot do. Furthermore there is no point in trying to compete with the computer in those spheres in which it excels, as here it is vastly superior to the human mind; I refer naturally to the ability of the computer to store vast amounts of information and its ability to regurgitate this information on demand. Surely then it is logical to use organic synthesis as the vehicle for teaching organic chemistry. It is true that Wipke has developed his method of "Computerised Synthesis",² but it is still only an aid to the organic chemist, still only a means, albeit a very sophisticated one, of storing and disseminating information.

I am convinced that in this day of the information explosion, when it is only possible to cover a minute percentage of any subject, the best way to teach organic chemistry, the best way to teach students to think within the subject, is via organic synthesis, although it will naturally be necessary for them to have certain background knowledge if this is to be done effectively. I define organic synthesis as "synthetic processes for the formation of organic molecules, in particular the formation of carbon-carbon bonds, and all the factors which influence them". At the teaching level, one naturally considers available methods, at the research level one develops new methods, or puts old methods to new uses. While few can claim to have developed organic synthesis to an art in the

same way as the likes of Woodward, Eschenmoser and Corey, nevertheless over the past fifty years organic synthesis has become much more sophisticated. The most important trend is an increase in the selectivity of the reactions used, although they are often a long way from achieving the ideal of one product in quantitative yield. In achieving greater selectivity it has been necessary to replace the "brute-force" methods of the past with methods which require much milder conditions. In recent years particular attention has been paid to stereoselectivity as it is the separation and identification of stereoisomers that is often the most difficult problem in a synthetic sequence. I have purposely used the more general term "stereoselectivity" as it includes "stereospecificity" and thus avoids confusion.³

Two areas of development in selective organic synthesis which are rapidly coming to the forefront and which are, I am convinced, destined to play an ever increasing role in this field, are

- (i) Bio-organic syntheses, including those using enzymes, of the type defined by van Tamelen⁴ and possibly best illustrated by the work of van Tamelen and others on the conversion of squalene to lanesterol.⁴
- (ii) Syntheses involving organometallic compounds as intermediates.

It is the latter which forms the main subject of my lecture this evening. Organometallic chemistry is probably the fastest growing branch of chemistry, the volume of literature doubling at least twice during the twelve year period 1956-1968,⁵ as compared with a doubling period for chemistry itself of approximately 15 years.⁶ It is not just a growth of volume, however, but also a growth of importance as indicated by the fact that in 1969 it was recommended to the Scientific Research Council in the United Kingdom that funds be made available for an additional 120-150 research workers in this field. This occurred at a time when it was expected that funds for non-organometallic chemical research would probably be cut by some 20%.⁷

Although there are many types of compounds that may be classed as organometallic, to the synthetic organic chemist, who is primarily concerned with the formation of carbon-carbon bonds, it is those compounds which contain a carbon-metal sigma-bond which are most important although this is not always the case.⁸ I will confine my remarks to this group of compounds.

Although it is popular to argue⁹ as to who prepared the first organometallic compound, I feel that this was settled once and for all when Hodgkin and her group at Oxford showed¹⁰ that the naturally occurring vitamin B₁₂ coenzyme molecule contained a carbon-cobalt bond. This is the only known case of a carbon-metal bond occurring in nature and hence these compounds provide the organic chemist with synthetic

intermediates not generally available to living systems. While it might be over imaginative to suggest that one day organometallics will give the bench chemist the same sort of synthetic control that enzymes exercise in living systems, I think it is reasonable to suggest that they will go some way to affording control of this nature. In fact there is already evidence available to this effect. Thus Ollis *et al.*¹¹ have shown that the thallic acetate oxidation of chalcones, which involves an organo-thallium intermediate, gives isoflavones, the same products as the biosynthetic process. There is no other chemical analogy for this process and these authors state (and I quote) "it is recognised that the oxidation by thallic acetate is a remote model for the enzyme controlled biosynthesis of isoflavones from chalcones, and yet the general features of both processes correspond". Certainly organometallic compounds have tremendous potential as intermediates in organic synthesis.

Let us consider some of the reasons why organometallic compounds are potentially so useful, particularly in reactions in which selectivity in one form or another is either desirable or even essential:-

(1) With the exception of the heavier alkali metal compounds most carbon-metal bonds are considered to be covalent. However, because of electronegativity differences the bonds do possess some ionic character and they are normally assumed to undergo reactions in which the organic moiety is transferred to the substrate as a carbanionic species. This is illustrated by the generally accepted mechanism for the addition of a Grignard reagent to a carbonyl group, that is the mechanism proposed by Ashby,¹² shown in figure 1.

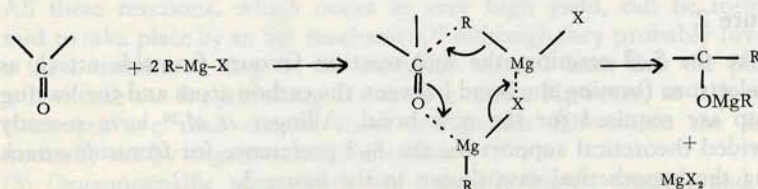


Figure 1

The reaction takes place by a cyclic mechanism, one alkyl group, with the electron pair forming the carbon-metal bond, being transferred to the carbonyl carbon atom. (For clarity I have omitted complexing solvent molecules from all the structures. By doing this I in no way intend minimising the importance of the role of the solvent in these reactions. Similarly all organometallic compounds will be shown as monomers and in their generally accepted form; again, I am fully aware that many exist as aggregates¹³ and in some cases there is considerable

controversy even over the structures of the monomers.¹²⁾ Not only do these compounds afford a means of generating potential carbanions as shown, but also of generating carbanions which do not require an activating group such as the carbonyl group on adjacent carbon atoms. (We will see later that not all reactions of organometallic compounds involve carbanionic intermediates.)

(2) As might be expected of potential carbanions, organometallic compounds undergo electrophilic substitution reactions at carbon, the so-called S_E reactions. Unlike their nucleophilic counterparts the unimolecular reactions, S_E1 , are extremely rare and are only known to take place under extremely polar conditions and with compounds in which the charge on the intermediate carbanion is highly stabilised.¹⁴ The commonest reactions are the bimolecular reactions, S_E2 , and internal reactions, S_Ei , the former being favoured by polar solvents, while the latter are favoured by non-polar systems in which the ligand plays a very important role. Both these reactions take place with retention of configuration as indicated by the respective transition states¹⁵ shown in figure 2.

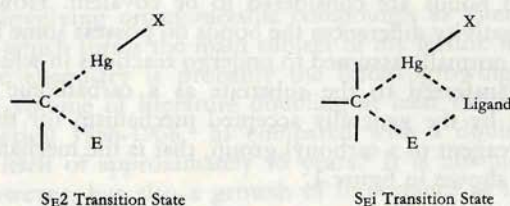


Figure 2

Unlike the S_N2 reaction, the S_E2 reaction favours frontside attack as the electrons forming the bond between the carbon atom and the leaving group are required for the new bond. Allinger *et al.*¹⁶ have recently provided theoretical support for the S_E2 preference for frontside attack using the hypothetical case shown in the figure 3.

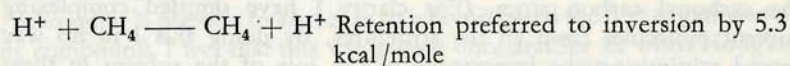
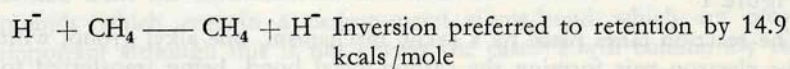


Figure 3

Thus virtually all electrophilic substitution reactions involving organometallic intermediates take place with retention of configuration, and

what is more important the reactions take place without racemisation. Brown¹⁷ has taken full advantage of this in his many synthetic procedures using organoboranes as intermediates, reactions which also illustrate the versatility of these compounds, as shown in figure 4.

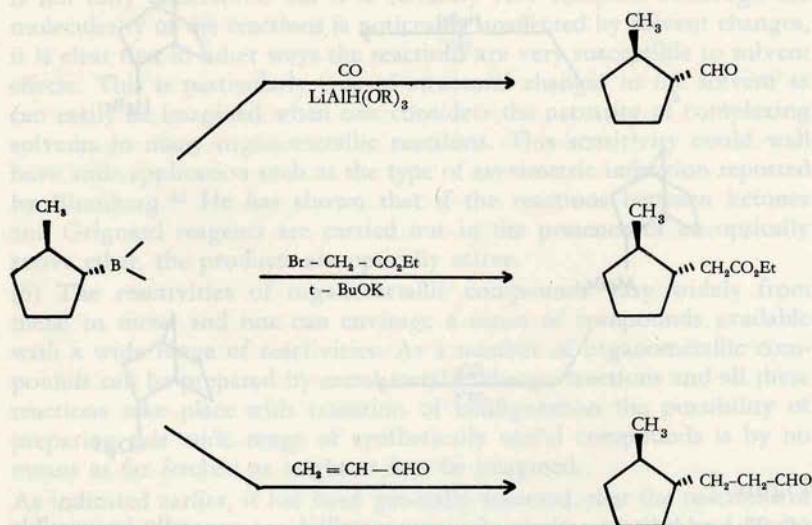


Figure 4

All these reactions, which occur in very high yield, can be formally said to take place by an S_Ei mechanism¹⁷ although they probably involve a three membered ring in the transition state. I trust that the purists will excuse me for including boron as a metal. However, as it is more electropositive than carbon these compounds fall within the limits normally set by organometallic chemists.¹⁸

(3) Organometallic compounds are generally highly reactive and this makes reactions with comparatively unreactive substrates possible, and generally results in high yields. Even more important is that reactions can generally be carried out under very mild conditions which reduces the possibility of isomerisation of either the starting material, the product or, and probably most important, the organometallic compound itself. Thus Roberts has shown¹⁹ that although the activation energy for the inversion of alkyl magnesium chlorides is only of the order of 11 kilocalories per mole, and these compounds undergo rapid inversion at room temperature, they are configurationally stable at -70° Centigrade. But the reactivity of these compounds even at very low temperatures

allows reactions to be carried out under conditions in which inversion does not take place, as illustrated by the work of Jensen *et al.*²⁰ shown in figure 5.

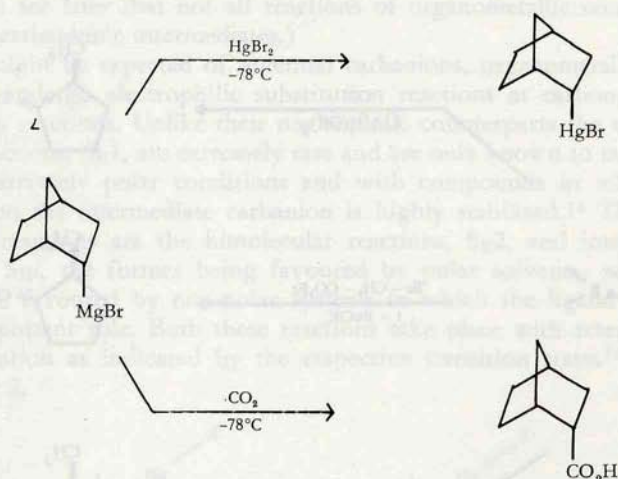


Figure 5

(4) The addition reactions of organometallics are generally irreversible which results in kinetic control. In some cases this allows for the exclusive formation of the less stable isomer, as illustrated by an example from House's²¹ work shown in figure 6.

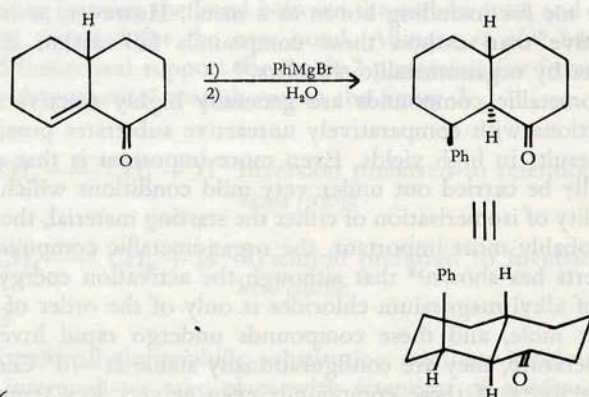


Figure 6

Attack takes place parallel to the axis of the p-orbitals of the unsaturated system resulting in a product in which the phenyl group is in the energetically less favourable axial conformation as shown.

(5) The role of the solvent in the reactions of organometallic compounds is not fully understood but it is certainly very complex. Although the molecularity of the reactions is noticeably unaffected by solvent changes, it is clear that in other ways the reactions are very susceptible to solvent effects. This is particularly true of structural changes in the solvent as can easily be imagined when one considers the necessity of complexing solvents in many organometallic reactions. This sensitivity could well have wide application such as the type of asymmetric induction reported by Blomberg.²² He has shown that if the reactions between ketones and Grignard reagents are carried out in the presence of an optically active ether, the products are optically active.

(6) The reactivities of organometallic compounds vary widely from metal to metal and one can envisage a series of compounds available with a wide range of reactivities. As a number of organometallic compounds can be prepared by metal-metal exchange reactions and all these reactions take place with retention of configuration the possibility of preparing this wide range of synthetically useful compounds is by no means as far fetched as might at first be imagined.

As indicated earlier, it has been generally assumed, that the reactions of organometallic compounds, when carried out in solution and under mild conditions, take place by mechanisms which involve heterolytic fission of the carbon-metal bond. (These reactions must not be confused with reactions carried out at elevated temperatures in the vapour phase or non-polar media such as the reaction of lead tetraethyl in the internal combustion engine, or those in which homolysis is induced by some process such as photolysis. All these naturally involve radical intermediates.) However, in the last few years, evidence has come to light which suggests that a number of reactions involve homolytic bond fission. Even in the case of alkyllithium compounds, normally considered to have a fairly high degree of ionic character, there is an abundance of evidence²³ to show that the reaction with alkyl halides takes place by a radical mechanism. This was most convincingly demonstrated by Ward and Lawler²⁴ who in fact used this reaction as a model in developing C I D N P (chemically induced dynamic nuclear polarisation), or to put it another way, the detection of the interaction between radicals by n.m.r., even when concentrations are too low for them to be detected by an e.s.r. spectrometer.²⁵ An example of the reaction is shown in figure 7.

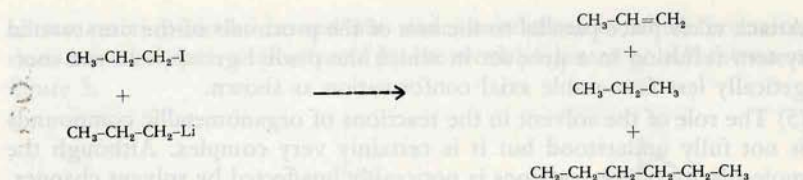


Figure 7

In another pioneering paper Russell *et al.*,²⁶ although not the first to propose the mechanism, put the reaction between carbanions and electron acceptors on a sound basis. They showed that n-butyl magnesium bromide can act as a one-electron transfer agent in its reaction with benzophenone, as shown in figure 8.

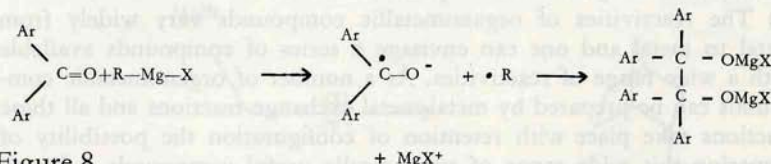


Figure 8

This reaction, to give a radical anion is generally limited to cases where normal attack is sterically hindered.

Gough and Dixon have shown²⁷ that in reactions between Grignard reagents and allyl halides, the electron density of the alpha carbon atom of the Grignard is lower in the transition state than in the ground state, and they explain their results in terms of the mechanism shown in figure 9.

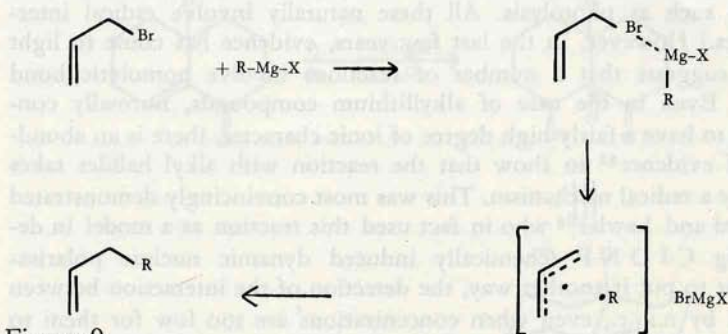


Figure 9

Recently, Brown has reported²⁸ that the reactions between organobo-

ranes and alpha,beta-unsaturated aldehydes and ketones of the type shown in figure 10

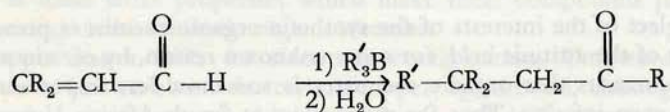


Figure 10

are completely inhibited by radical scavengers, and those reactions which for steric reasons do not take place readily, are catalysed by radical generators.

Thus we see, that even in the case of those classes of compounds most widely used in organic synthesis, namely organolithium, -magnesium and -boron compounds, there is still considerable doubt as to the factors that influence cleavage of carbon-metal bonds. In fact knowledge of the nature of the bonds is limited. It is here that we require the assistance of our inorganic colleagues.

In this connection I would like to digress for a moment.

It is popular to speak of the "breaking down of the traditional barriers between the different branches of chemistry" and organometallic chemistry is often cited, quite correctly, as an example of this process. While every effort to unite all branches of chemistry into the single subject that it is, in particular from the point of view of students, is to be highly recommended, let us not think that in any way the magnitude of the subject is reduced by doing this, or that things are made any easier. In fact, in order to study organometallic chemistry in depth, a detailed study of both organic chemistry and inorganic chemistry is required, something which is rapidly becoming less and less possible. It is therefore essential that organic and inorganic chemists co-operate, both at the teaching and the research level.

Unfortunately, as far as organometallic chemistry is concerned, the interests of the synthetic organic chemist have been to a certain extent ignored by inorganic chemists. Thus in two recently published advanced texts,²⁹ which my colleagues assure me are amongst the best available, no discussion of the carbon-copper sigma-bond is included. Yet it was in 1859 that Böttger first reported³⁰ the formation of a copper acetylide and these compounds are widely used in organic synthesis as evidenced by a recent review³⁰ containing 127 references. Similar neglect at the research level is shown by a recent symposium³¹ on "Bonding

in Metallo-organic Compounds" when discussion on the carbon-metal sigma-bond was almost entirely restricted to metal carbonyls. In contrast, at a recent symposium³² on "Co-ordination Complexes", one of the plenary lectures was delivered by Eschenmoser, a synthetic organic chemist.

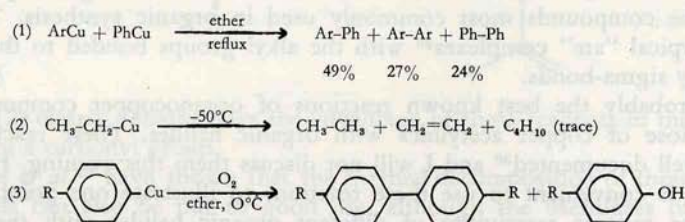
This neglect of the interests of the synthetic organic chemist is presumably part of the attitude held, for some unknown reason, by certain non-organic chemists that organic chemistry is somehow less important or possibly even inferior. Thus for many years at South African Universities, Chemistry I courses either omitted organic chemistry completely or included it in a limited way in special courses for medical students and the likes. It is doubtful even today if it always gets its full share of teaching time at this level.

Even more serious is the neglect of organic chemistry in our schools. Until recently, no organic chemistry was included in the matriculation physical science syllabus. In the new syllabus, published in draft form for the first time in 1965, and intended for examination at the matric level for the first time in 1970, organic chemistry was included, albeit to a limited extent, for the first time. However, at the request of the Departments of Education, permission has recently been granted³³ by the Joint Matriculation Board, for certain sections of the new syllabus to be excluded for examination purposes for 1970 and 1971 at schools under Departmental control. One of these sections includes all the organic chemistry. I ask, "Is it fair to our school children, in particular those who will never have the opportunity of studying chemistry again, to exclude all the organic chemistry when one considers that roughly 95 per cent³⁴, I repeat 95 per cent, of all known chemical compounds belong to this one class?" Furthermore, it is to this class that many of the things of this modern day and age belong; one thinks of plastics, synthetic fibres, modern drugs and petroleum to mention a few of the things that we come in contact with or which make headline news every day. The permission for organic chemistry to be excluded from the syllabus for examination purposes must not be allowed to be extended beyond this two year period.

Returning to organometallic chemistry, I would like to consider some recent developments in the use of organocopper compounds as intermediates in organic synthesis. These developments which have been reported over the past four years, will illustrate the points that we discussed earlier.

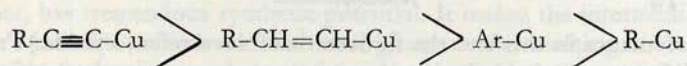
I have chosen copper because it is something of a rebel, a transition metal which in some ways resembles the alkali metals and yet has certain noble metal characteristics. It is also a rebel in the organometallic world. In

Organocopper compounds are generally unstable and, like many other organometallic compounds, on thermal decomposition give products typical of radical reactions. They are also extremely susceptible to oxidation, with products again indicating radicals. Examples of these reactions³⁸ are given in figure 11.



Reaction (2) in addition to showing that the term "thermal decomposition" is purely relative, suggests that there is some deviation from normalcy for free radical reactions in that only a trace of butane is formed.

The relative stabilities of these compounds, and I must admit that this is very qualitative and is based largely on the ease of thermal decomposition, is indicated in figure 12.



This sequence, which is very susceptible to substituent effects, could be due to the effect of $p-\pi$ interactions utilising the vacant $4p$ orbitals of the copper, differences in s -character of the bonding orbital of carbon,

interaction between the filled 3d orbitals and anti-bonding π -orbitals or a combination of these three. In the case of oxidation, however, all organocopper compounds are extremely sensitive and it is necessary for all reactions to be carried out with the rigorous exclusion of oxygen. Most organocopper compounds are insoluble, even in ether type solvents, and this presents serious experimental problems because of their instability. They are therefore usually prepared as soluble complexes³⁹ of the type illustrated in figure 13.

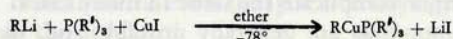
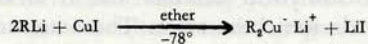


Figure 13

(These reactions also illustrate the usefulness of metal-metal exchange.) These complexes, which probably exist as aggregates in solution, are found to be more reactive than the parent organocopper compounds. The first of the two classes shown, the lithium di-organocuprates, are the compounds most commonly used in organic synthesis. They are typical "ate" complexes⁴⁰ with the alkyl groups bonded to the copper by sigma-bonds.

Probably the best known reactions of organocopper compounds are those of copper acetylides with organic halides. These reactions are well documented³⁰ and I will not discuss them this evening. However, it is convenient to use these reactions to illustrate one point, namely the relative reactivities of different organic halides with these compounds,⁴¹ as shown in figure 14.

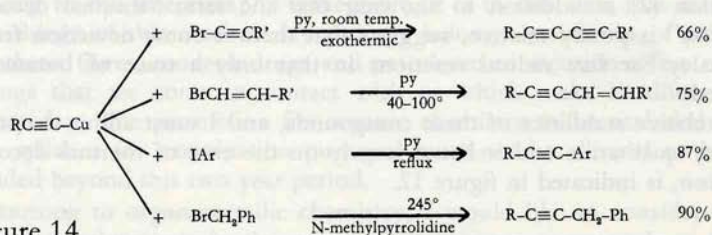


Figure 14

(All percentages in this and the figures that follow refer to yields.) From these differences it is clear that the reactions do not involve a simple nucleophilic displacement of halogen as the order of reactivity would be reversed if this were the case.

The use of vinylcopper compounds as synthetic intermediates is of much more recent development. However, Vig *et al.*⁴² have certainly demon-

strated their potential in reactions with the carbon-halogen bond, particularly in the field of terpenoid synthesis, as shown in figure 15.

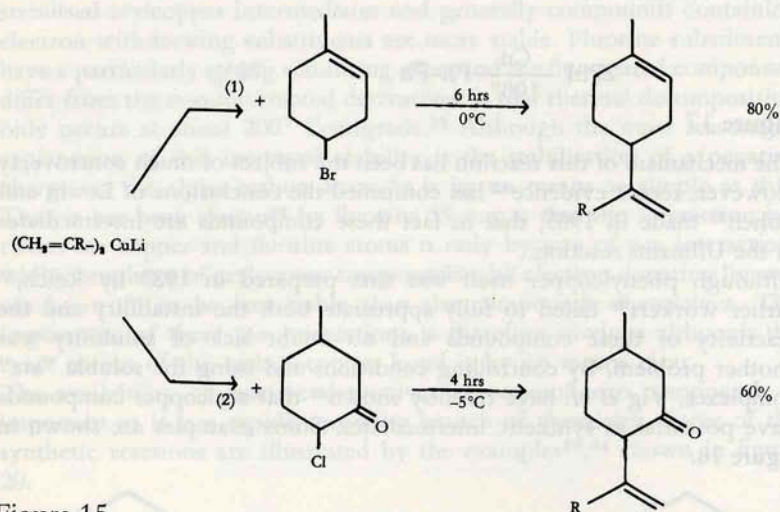


Figure 15

Reaction (2) clearly demonstrates the advantage of these reagents in the presence of a carbonyl group.

Whitesides *et al.*⁴³ have shown that the thermal decomposition of these compounds can also be put to good use, although the usefulness of this reaction is limited to the synthesis of symmetrical compounds. An example is shown in figure 16.

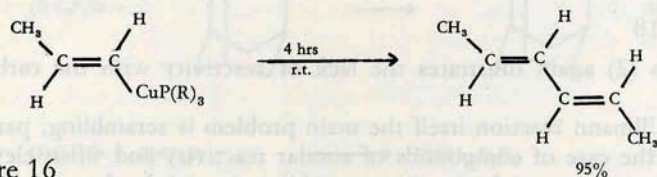


Figure 16

The stereospecificity of the coupling, which also occurs with the *trans* isomer, has tremendous synthetic potential. It makes the intermediacy of "free" radicals unlikely as this would require the reaction to be considerably faster than inversion of the vinyl radical, an inversion that is estimated to occur $10^8 - 10^{10}$ times per second.⁴³ However, this does not preclude the participation of caged radicals or some other process involving homolytic bond cleavage and complexed intermediates.

Arylcopper compounds have been used for years in organic synthesis

although it has only recently been confirmed that this is the case. I refer to the Ullmann reaction, first reported in 1904.⁴⁴ An example is shown in figure 17.

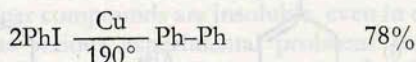


Figure 17

The mechanism of this reaction has been the subject of much controversy. However, recent evidence⁴⁵ has confirmed the conclusions of Lewin and Cohen⁴⁶ made in 1965, that in fact these compounds are intermediates in the Ullmann reaction.

Although phenylcopper itself was first prepared in 1923 by Reich,⁴⁷ earlier workers⁴⁸ failed to fully appreciate both the instability and the reactivity of these compounds and no doubt lack of solubility was another problem. By controlling conditions and using the soluble "ate" complexes, Vig *et al.* have recently shown⁴⁹ that arylcopper compounds have potential as synthetic intermediates. Some examples are shown in figure 18.

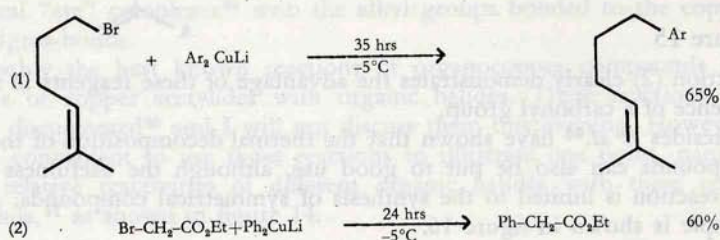


Figure 18

Reaction (2) again illustrates the lack of reactivity with the carbonyl group.

In the Ullmann reaction itself the main problem is scrambling, particularly in the case of compounds of similar reactivity and when elevated temperatures are used. As this scrambling is mainly due to copper-halogen exchange the availability of arylcopper intermediates is no solution. This exchange has been clearly illustrated by Nilsson *et al.*⁵⁰ using deuterated compounds as shown in figure 19.

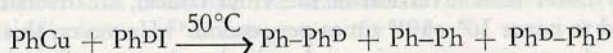


Figure 19

Thus a general method for the unambiguous synthesis of unsymmetri-

cal biaryls still remains as one of the great challenges of organic synthesis.

The possibility of scrambling is considerably reduced by the use of stabilised arylcopper intermediates and generally compounds containing electron withdrawing substituents are more stable. Fluorine substituents have a particularly strong stabilising effect and the fluorinated compounds differ from the non-fluorinated derivatives in that thermal decomposition only occurs at about 200° Centigrade.⁵¹ Although the most reasonable explanation of this increased stability is the stabilisation of a negative charge on the alpha carbon atom, it is by no means as simple as this. Thus it has been shown⁵² by fluorine 19 n.m.r. that the interaction between the copper and fluorine atoms is only by way of p- π interaction, while complexes of arylcopper compounds with electron donating ligands are known⁵³ to be less stable than the compounds themselves. The importance of these p- π interactions is therefore obvious although the exact nature of the carbon-copper bond is by no means clear.

The availability of reactive derivatives of organofluoro compounds is important as it is a rapidly growing branch of chemistry. Some of the synthetic reactions are illustrated by the examples^{52, 54} shown in figure 20.

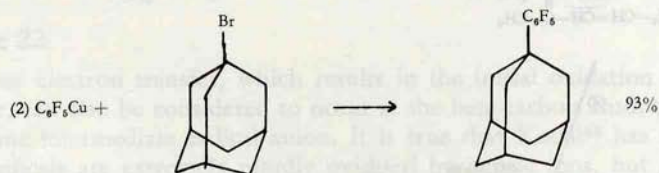


Figure 20

Reaction (1) is of interest in that it affords a method for the synthesis of compounds which, because of the effect of the fluorine substituents, are not available by the normally used Friedel-Crafts acylation. It would appear that nucleophilic attack is unlikely in reaction (2) although Schleyer *et al.*⁵⁵ have provided evidence of the existence of the adamantyl carbonium ion even though it does occur at a bridge-head. The situation is

further confused by the fact that in reaction (3) the benzyl carbonium ion has been quantitatively intercepted, while it has been reported⁵⁶ that lithium diphenylcuprate does not react with adamantyl bromide. Is it possible that different mechanisms might be operating in these various reactions?

Probably the most interesting chemistry of the organo-copper compounds has resulted from a study of the alkylcopper compounds. They were first characterised by Gilman *et al.*⁵⁷ in 1952, but in fact they have been unknowingly used in organic synthesis since 1941 when Kharasch *et al.*⁵⁸ showed that cuprous salts effected the addition of Grignard reagents to alpha,beta-unsaturated ketones. However, it is only recently that House *et al.*⁵⁹ have confirmed the earlier suggestions⁶⁰ that the increase in percentage of 1,4-addition is due to the formation of alkylcopper intermediates. The results obtained by these authors illustrate dramatically the reactivity of these copper compounds as shown in figure 21.

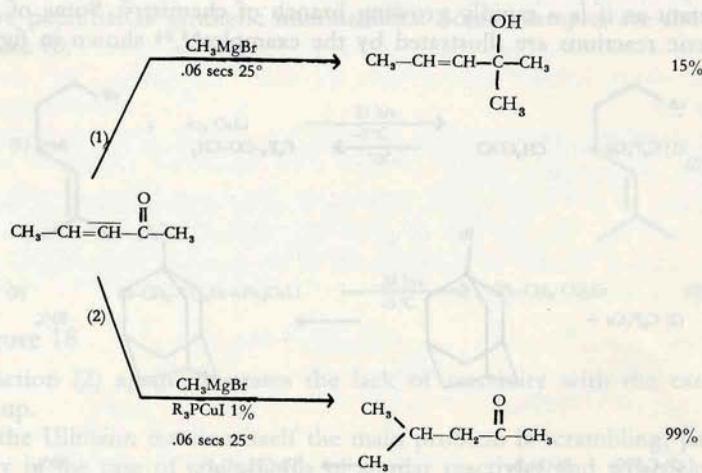


Figure 21

(Hydrolysis steps are omitted for clarity.) The normal reaction of Grignard reagents is mainly 1,2-addition as shown in reaction (1), but in the presence of cuprous salts, added in this case as the soluble trialkylphosphine complex, 1,4-addition takes place exclusively. Reaction (2), which involves initial formation of complexed methylcopper, is so fast that it occurs with the complete exclusion of reaction (1), itself a reaction with a half life of less than 0.2 seconds. Furthermore the initial concen-

tration of the methylcopper, which has to be reformed many times during the course of the reaction, is only 1% that of the Grignard reagent.

From an exhaustive investigation of this reaction, House and his group⁶¹ have arrived at the following conclusions:

- It is necessary for the copper to be in the "ate" form.
- The reaction does not involve a cyclic transition state.
- Attack takes place parallel to the plane of the p-orbitals of the unsaturated system.
- No "free" radicals are formed during the reaction as the presence of isoprene in the reaction mixture does not effect the result.

From this they suggest the mechanism shown in figure 22.

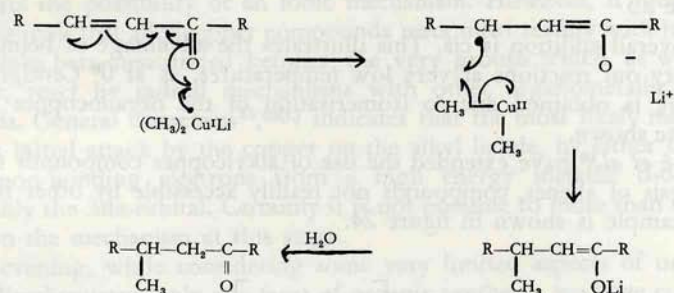


Figure 22

The one electron transfer, which results in the initial oxidation of the copper, can also be considered to occur at the beta-carbon atom to give the same intermediate radical anion. It is true that Kochi⁶³ has shown that radicals are extremely rapidly oxidised by cupric ions, but as this oxidation does not take place with undissociated cupric ions, it is reasonable to assume that it does not occur in this case.

Marshall and Roebke⁶² have studied the effect of bulky substituents in this reaction. They have found that it is steric interaction in the transition state rather than steric hindrance to the attacking reagent that influences the reaction, and that the transition state is close to the product. These results fit House's mechanism well if one is prepared to accept the not unreasonable assumption that the carbon atom bearing the odd electron is tetrahedral, albeit flipping rapidly.

The closely related addition of alkylcopper reagents to acetylenic esters has been shown by both Siddall *et al.*⁶⁴ and Corey and his group⁶⁵ to

provide a stereoselective route to tri- and tetra-substituted olefins. An example is shown in figure 23.

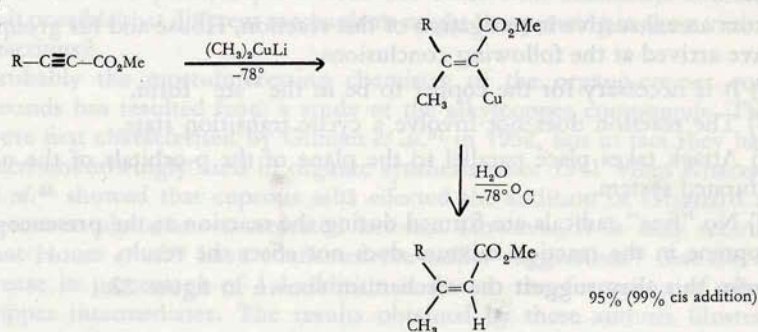


Figure 23

The overall addition is cis. This illustrates the advantage of being able to carry out reactions at very low temperatures, as at 0° Centigrade a mixture is obtained due to isomerisation of the organocopper intermediate shown.

Crabbé *et al.*⁶⁶ have extended the use of alkylcopper compounds to the synthesis of allenes, compounds not readily accessible by other routes. An example is shown in figure 24.

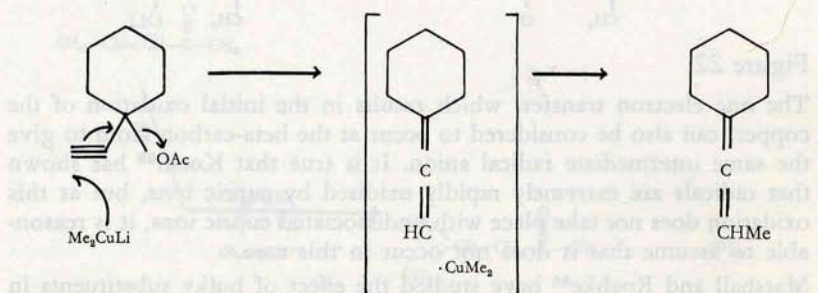


Figure 24

These authors propose a mechanism involving a one electron transfer similar to that discussed previously. They suggest that the reason for lack of stereoselectivity is that the intermediate shown cannot maintain its geometry. Presumably this is due to the higher temperature required to effect reaction.

These same authors⁶⁷ and Siddall *et al.*⁶⁸ have also investigated the related reaction with allylic acetates and although the predominant products

can be explained in terms of an allylic rearrangement related to the above reaction, isomeric mixtures are also obtained in this case.

The reactions of alkylcopper compounds with aryl, alkenyl and alkyl halides and tosylates have been investigated by Corey,⁶⁹ House⁵⁶ and Whiteside⁷⁰ and their respective groups. Generally the results are much the same as those for aryl- and vinylcopper compounds although copper-halogen exchange can take place even more readily. To a certain extent this difficulty has been overcome by the use of excess of one reagent, or by oxidation. Most interesting are the reactions with alkyl halides and tosylates as these reactions have given some indications of the mechanism of the reaction. It has been found that under suitable conditions the reactions take place with 85 - 90% inversion of configuration at the carbon atom alpha to the iodide, and with greater than 98% retention of configuration at the carbon atom alpha to the copper. This certainly suggests the possibility of an ionic mechanism. However, it must not be forgotten that alkylcopper compounds react most readily with halides and alpha,beta-unsaturated ketones, the very groups which, as we saw earlier, react by radical mechanisms with other organometallic compounds. General consensus^{56, 69(c)} indicates that the most likely mechanism is initial attack by the copper on the alkyl halide, by either one or two non-bonding electrons from a high energy metallic d-orbital, probably the 3dz-orbital. Certainly it is not possible to more than speculate on the mechanism at this stage.

This evening, while considering some very limited aspects of organometallic chemistry, only one facet of organic synthesis, we have covered the chemistry of a wide range of compounds and a number of reaction types. This surely supports my thesis that it is logical to use organic synthesis as the vehicle for teaching organic chemistry. I have also tried to give some idea of the potential of organometallic compounds as intermediates in organic synthesis. Do not think that the advantages are limited to laboratory syntheses; they also have tremendous potential in the industrial field as they have the particular economic advantage that the metals used are readily recoverable. However, as has been equally evident, there is still much that is not understood about the chemistry of organometallics, and the full advantage of these intermediates will not be realised until the basic chemistry of these compounds is understood.

South Africa is a country that is in the process of establishing its industrial independence. If this is to be achieved in what is one of the fastest growing branches of chemistry, or any branch of chemistry for that matter, now is the time to start basic research in this field, research aimed at the understanding of the chemistry of these compounds, research aimed

at the long term benefits. Without a research programme of this nature, industrial independence cannot be established. This basic research should be carried out at the universities, at the research institutes and in industry. It is only by close co-operation of all three particular interests that the full benefit will be reaped.

In conclusion, Mr Vice-Chancellor, I would like to take this opportunity of thanking the University of South Africa, of thanking my colleagues in the Department of Chemistry who have always given organic chemistry its share of time, and of thanking my wife.

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