

EVIDENCE FOR A REVERSIBLE d, π^* -COMPLEXATION, β -CUPRATION SEQUENCE IN
THE CONJUGATE ADDITION REACTION OF GILMAN REAGENTS WITH α, β -ENONES.

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Summary: *In situ* trapping of reaction intermediates combined with stereochemical studies of the reaction of lithium dimethylcuprate with enones provides evidence for a pathway involving d, π^* -cuprate-enone and copper(III) β -adducts as important intermediates in cuprate-mediated conjugate addition of carbon.

Despite the increasingly important role in synthesis of copper-mediated conjugate addition of carbon to α, β -enones,^{1,2} the mechanistic details are unclear. The intermediacy of a copper(III) β -adduct, which can undergo C-C bond formation by reductive elimination, is widely accepted on the basis of analogy even though direct experimental support is lacking. In addition, although a single electron transfer (SET) from the organo-copper reagent to the enone has often been proposed as an initial step, it is not known whether SET is obligatory, incidental, or significant only in special cases. Two outstanding recent papers provide evidence that complexation of organocuprates (Gilman reagents) with enones may be an important early event.^{3,4} Kinetic studies utilizing stoppedflow spectroscopy have implicated an intermediate complex which can give rise to product via a copper(III) β -adduct.³ That the complex involves binding of copper to the π -system was shown by ^{13}C and ^1H nmr investigations of mixtures of organocopper reagents and cinnamate esters at low temperatures.⁴ It has been pointed out that the d -orbitals of copper in cuprate reagents allow the formation of metastable d, π^* -complexes involving interaction of copper as a d -base with the α, β and carbonyl carbons (π_3^*) of the enone acting as a π -acid.⁵ In this note we report the results of chemical studies which demonstrate the importance of reversible π -complexation and β -cuprio adduct formation in the conjugate addition of carbon to α, β -enones. This evidence derives partly from the use of combinations of organocuprate reagents and chlorotrimethylsilane which are discussed in detail in a following publication.⁶ We have found that organocuprates and chlorotrimethylsilane are mutually compatible at -78° and also that conjugate addition reactions to enones are accelerated by chlorosilane.

α, β -Enones possessing a γ -oxygen or amide nitrogen substituent exhibit more complex reactivity towards cuprates than do simple α, β -enones. Depending on the anionic leaving tendency of the γ -heteroatom, either normal conjugate addition (with poorer γ -leaving groups) or reductive cleavage of the γ -heteroatom to form a β, γ -unsaturated ketone (with better γ -leaving groups) can occur.⁷ The conjugate addition process generally takes place with the addition of carbon to C(β) in the anti sense relative to the heteroatom at C(γ).⁹ In our view the preference for anti stereochemistry probably arises from a stereoelectronic effect in which the γ -heteroatom removes electron density hyperconjugatively from the $d(\text{Cu}), \pi_3^*$ -complex or the Cu(III) β -adduct with maximum stabilization occurring in the anti geometry.⁵ Other explanations for the anti preference based

on Felkin's generalization⁸ have been offered.⁹ The γ -oxygen-containing spiro enone 1 was selected as an interesting test case for mechanistic studies because of its well-defined geometry and the absence of purely steric factors favoring anti stereochemistry.

The synthesis of 1 was accomplished as follows. Methyl 3-(4-methoxyphenyl) propionate (from the acid, 2, 2-dimethoxypropane, methanol, and *p*-toluenesulfonic acid at reflux) was reduced to the corresponding primary alcohol 2 (LiAlH₄, ether, >95% yield), which upon Birch reduction (lithium, 2 : 1 : 1 ammonia - tetrahydrofuran (THF)-*t*-butyl alcohol, -33°) followed by acid hydrolysis (oxalic acid catalyst in 1 : 1 THF-water) resulted in the β, γ -enone 3. Crude enone 3 was directly epoxidized using *m*-chloroperbenzoic acid in CH₂Cl₂ at 0° and the product was converted without isolation to diol 4 (70% from 2) by addition of triethylamine to the cold solution. Cyclization of diol 4 was effected by reaction with 1.5 equiv of triflic anhydride and 3 equiv of diisopropylethylamine in CH₂Cl₂ at -78° to give spiro enone 1 in 81% yield.

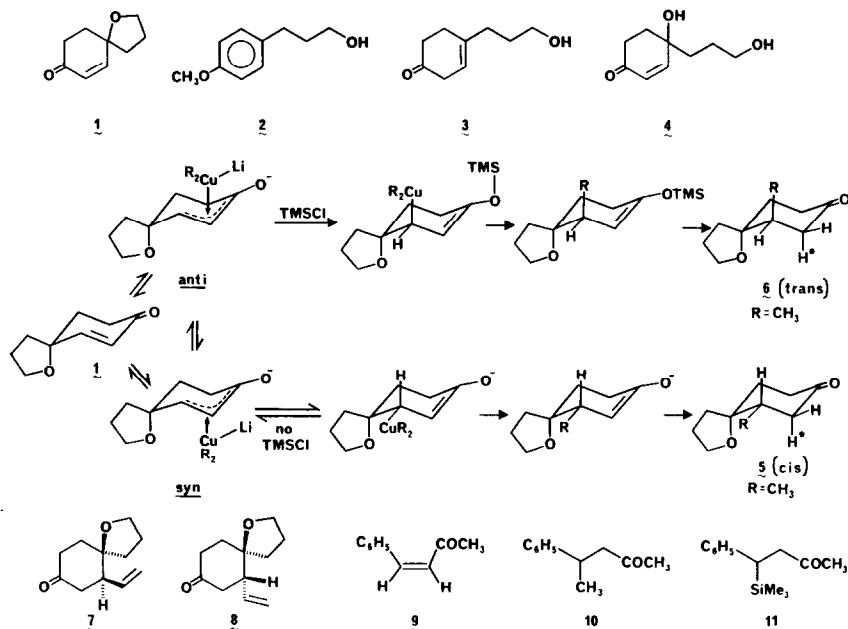
Reaction of 1 with lithium dimethylcuprate in THF, initially at -78° with gradual warming thereafter to 0°, was homogeneous throughout and gave a mixture (61%) of the two possible adducts, 5 (cis) and 6 (trans) in a ratio of 92 : 8. The stereochemistry of 5 and 6, the stable conformers of which were determined by molecular mechanics calculations¹⁰ to be as displayed herein, was assigned from the observed vicinal pmr coupling constants of the axial α -proton (H*) vicinal to methyl (for 5, J=13.0 Hz; for 6, J=5.3 Hz).¹¹

This initial result was fascinating, since we had expected a predominance of anti addition product 6. One possible interpretation of this finding was that the product ratio might be a consequence of rapid reversibility of copper-enone complex formation and a much faster rate of product formation from the cis d, π^* -complex (syn O/Cu complex). This idea suggested a study of the reaction in the presence of chlorotrimethylsilane (TMSCl). In fact, at -78° in the presence of 5 equiv of TMSCl the reaction was greatly accelerated (complete in less than 2 min) and afforded only anti product (ratio 6 : 5 >99 : 1) in 70% yield. *t*-Butyldimethylsilyl triflate and chloride also produced strong acceleration and caused the anti product 6 to predominate by >99 : 1. In 20 : 1 toluene-THF the (homogeneous) reaction of 1 with lithium dimethylcuprate at -78° was non-stereoselective (5 : 6 = 1 : 1), but became specific for 6 in the presence of TMSCl.

In ether the reaction of 1 and lithium dimethylcuprate became heterogeneous at -78° with the development of a yellow precipitate which proved to be a complex of these two reactants. The complex was isolated by centrifugation at -78° and removal of the supernatant liquid. The complex could be partially dissolved in THF at -78° and transformed by addition of TMSCl exclusively into the trans adduct 6. Reaction of this solid complex in ether suspension either in the absence or presence of TMSCl gave both 5 and 6 non-selectively. To the best of our knowledge this is the first case in which a cuprate-enone complex has been isolated and shown to be convertible to conjugate addition products. The fact that both 5 and 6 are formed from the insoluble complex in ether indicates that it may be a mixture of cis and trans forms.

Analogous results have been obtained for the reaction of 1 and lithium divinylcuprate in THF at -78°, a homogeneous system. In the absence of TMSCl the ratio of cis to trans vinyl adducts (7 and 8) was 44 : 56, whereas in the presence of TMSCl the trans isomer was the exclusive product (7 : 8 = <1 : 99).

The above results strongly support a mechanism in which 1 reacts with cuprates in a rapid and reversible manner to give cis and trans d, π^* -complexes with the latter predominating in THF solution. These stereoisomeric intermediates then go on at different rates to 5 and 6 at -78°. In the absence of TMSCl in THF the cis



d, π^* -complex goes on to *cis* copper (III) β -adduct and thence to product more rapidly than the predominating *trans* d, π^* -complex, perhaps for steric reasons. In the presence of $TMSCl$ the predominating *trans* complex is rapidly trapped and converted to **6**. It appears likely that most of the trapping occurs at the π -complex stage since its steady-state concentration is doubtless much greater than that of the copper (III) β -adduct.⁴ The accompanying equations summarize the postulated sequence.

If the $TMSCl$ -promoted conversion of **1** to the *trans* product **6** is indeed due to the trapping of *trans* d, π^* -complex, the question arises as to whether copper (III) β -adduct formation is normally (i.e., in the absence of $TMSCl$) a reversible process. To address this issue we have studied the interaction of *Z*-enone **9** with lithium dimethylcuprate under various conditions.¹²

The reaction of *Z*-enone **9** with 2 equiv of lithium dimethylcuprate in THF does not proceed measurably in 1 hr at -78° , but does give the 1,4-adduct **11** cleanly at 0° for 30 min. However, at -78° the *Z*-enone **9** undergoes cuprate induced isomerization to the more stable *E*-enone in just 15 min (to give the equilibrium mixture of 98% *E*- and 2% *Z*-enone) with no detectable 1,4-adduct **10** (270 MHz PMR analysis). Under the same conditions (-78° , 15 min, THF) in the presence of $TMSCl$ the reaction mixture contains 41% unreacted enones, ratio *Z* : *E* equals 95 : 5, and 59% of the enol TMS ether of **10**. Thus the presence of $TMSCl$ accelerates conjugate addition and prevents *Z* \rightarrow *E* isomerization. This must be due to the trapping of a common intermediate for both processes. That common intermediate is doubtless the copper (III) β -adduct whose formation must be reversible in the absence of $TMSCl$.

The reaction of *Z*-enone **9** with lithium dimethylcuprate in ether also led to rapid *Z* \rightarrow *E* equilibration at -78° in less than 30 min with no 1,4-methyl addition. However, in ether there was concomitant precipitation of a cuprate-enone complex. The complex was characterized (after isolation by centrifugation at -78°) by (1) reaction at -78° with $TMSCl$ in THF solution to form the TMS enol ether of **10**, and (2) reaction with THF-aqueous ammonium chloride to generate *Z*-enone **9** and its *E* isomer in a ratio of 2 : 98.

Cuprate-induced isomerization of a Z-enone to an E-enone has previously been reported by House and co-workers¹³ and ascribed to the reversible formation of a radical anion by electron transfer from cuprate to enone. Such a mechanism cannot explain the results outlined above for the chemistry of Z-enone 9 in the presence of lithium dimethylcuprate and TMSCl. We have generated the radical anion from E-9 in the presence of TMSCl by reaction at -95° in THF with lithium naphthalenide. The major product was the β -silyl ketone 11 (72%), a substance which was absent from the reactions of enone 9 with lithium dimethylcuprate in the presence of TMSCl.¹⁴

From the evidence described herein we conclude that: (1) the conjugate addition reaction of lithium dimethylcuprate with enones proceeds via reversible d, π^* -complex and copper (III) β -adduct formation (in that order), and (2) an initial electron transfer step from cuprate to enone is not obligatory. Studies are in progress to determine whether electron transfer can be an obligatory first step with certain Michael acceptors or cuprates. We believe that the use in situ of silyl electrophiles, as illustrated by the present study, is a powerful tool for the study of mechanisms of organometallic reactions.¹⁵

References and Notes

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- Both 5 and 6 were found to be more stable than the alternative chair forms by ca. 1.3 kcal/mole (Allinger MM-2 calculations with Mr. Stewart Rubenstein).
- The cis isomer 5 is less polar as determined by chromatographic mobility (both thin layer chromatography on silica gel and gas chromatography on a carbowax column) than the trans isomer 6.
- Z-enone 9 was prepared by Lindlar reduction of 4-phenylbutyn-2-one.
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- Although in principle the β -silyl ketone 11 could arise from the conversion of TMSCl to TMS anion and subsequent addition to enone 9, the reaction of TMSCl with lithium naphthalenide was considerably slower than the transformation of 9 to 11 at -95° .
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