Tetrahedron Letters,Vol.25,No.29,pp 3063-3066,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

d-ORBITAL STEREOELECTRONIC CONTROL OF THE STEREOCHEMISTRY OF S_N2' DISPLACEMENTS BY ORGANOCUPRATE REAGENTS

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Summary: The *anti* stereochemistry observed in organocuprate S_N2' displacements can be rationalized as a stereoelectronic effect arising from "bidentate" binding involving a d orbital of nucleophilic copper and π^* and σ^* orbitals of the substrate. The extension of this idea to other reactions of organocuprates including additions to acetylenes and enones is discussed.

Cuprate reagents show remarkable *anti* selectivity in S_N2' reactions for a wide variety of systems. Our recent study of the γ-displacements of optically active bromoallenes has underscored this *anti* preference,[1] but it has also been seen in almost all cuprate displacements of allylic[2] and propargyl systems,[3] including S_N2' opening of vinyl and acetylenic epoxides.[2g, 4] In fact, the only cases of clear *syn* predominance that do not involve chelation of the cuprate to the leaving group can be attributed to overriding steric constraints.[2c, g, 4j]

The consistency of this *anti* selectivity contrasts with the wide variability of S_N2' stereochemical preference observed with conventional carbon nucleophiles.[2g, 5] Taken together, the strong *anti* selectivity and the high rates of reaction of organocopper reagents as compared to other carbon nucleophiles in these systems[6] suggest that some special structural feature of nucleophilic Gilman reagents may play a pivotal role in S_N2' displacements. Any mechanistic scheme for cuprate S_N2' reactions must take into consideration both the probability of an equilibrium between species which differ with regard to aggregation or structure and also the possible occurrence of single electron transfer pathways. In the case of *anti* selective S_N2' reactions the latter possibility is clearly unlikely because it leads to the expectation of little or no stereoselectivity.

Unlike most carbon nucleophiles (*e.g.*, CN^-, EWG-stabilized anions, Grignard and organolithium reagents), nucleophilic organocopper(I) reagents contain a filled set of d orbitals. For this reason, nucleophilic displacements by d^{10} copper most likely will involve an electron pair in a sterically accessible high energy d orbital. The electron density in this orbital will have the usual binodal symmetry and will moreover be exceedingly diffuse due to electron-electron repulsion in the d^{10} system.[7] We propose that this diffuseness leads to "bidentate" overlap in allylic, allenic and propargylic systems such that the transition state for S_N2' attack has some S_N2 character. The binding in this transition state can be described as resulting from the simultaneous interaction of a copper d orbital with the LUMO (π^*) at the gamma carbon and, to a considerably smaller extent, with the antibonding orbital (σ^*) at the backside of the alpha carbon. Such binding is pictured in Fig. 1 for the simple allylic case. If the phasing of π^* (C=C) and σ^* (C-X) orbitals is appropriate for an S_N2' transition state, the symmetry of the d (Cu) orbital allows simultaneous binding between d (Cu), π^* (C=C) and σ^* (C-X) orbitals, as shown in Fig. 1. To the extent that the S_N2' transition state for organocuprate reactions includes a degree of S_N2-type binding, the anti pathway for S_N2' displacement will be preferred. Only 3-5 kcal./mole of net stereoelectronic[8] stabilization by the S_N2 binding component should be sufficient to account for the observed anti S_N2' preference, since other factors favoring syn stereochemistry can be expected to be relatively minor energetically. Clearly this argument also applies to allenic and propargylic systems. Thus, these cuprate displacements possess S_N2' and S_N2 character with the latter stereoelectronically[8] controlling the anti stereochemistry. Although the stereoelectronic explanation for preferential anti S_N2' displacement outlined herein neither implies nor requires any particular state of aggregation of the organocuprate reagent, it is fully consistent with structural information currently available.[9]

Recognition of the diffuseness of the nucleophilic Cu d orbital as well as the symmetry relationships involved with substrate LUMO orbitals also provides a rational and unifying view of other unique reactions of Gilman reagents. We outline briefly the logical extension of our ideas to (a) C-X/organocuprate cross coupling reactions,[10] (b) cis-addition of organocuprates to acetylenes,[11] and (c) conjugate addition reactions of organocuprates to enones.[12,13] Conceptual orbital combinations for the transition states of these processes are diagrammed in Fig. 2. Cross coupling of organocuprates to $C_{sp}3$ halides can occur by a normal S_N2 pathway in which a copper d lone pair interacts with the σ^* (C-X) orbital backside to the leaving group with resulting Walden inversion. Cross coupling of organocuprates to $C_{sp}2$ halides, however, is known[10] to occur with retention rather than inversion. This result can be understood in terms of the binding scheme shown in Fig. 2(a) where the d (Cu) electron pair enters the C-X antibonding lobe at X with a simultaneous bonding interaction between the developing electron pair at carbon and the same copper d orbital. In such a transition state, negative charge is transferred smoothly from copper to X and a carbon-copper bond is formed as the C-X bond is weakened, a concert which is made possible by the diffuseness and symmetry of the copper d orbital. The resulting organocopper (III) intermediate, $R_2CuR'\,X^{-}\,Li^{+}$ undergoes the usual reductive elimination (similarly facilitated by d (Cu) interactions) to form the cross coupling product RR'.

Cis addition of Gilman reagents to C≡C can be regarded as arising from unsymmetrical bidentate interaction of a d(Cu) orbital with a π^* orbital of the triple bond. The resulting structure (Fig. 2(b)) will vary in geometry and charge distribution depending on the acetylenic substrate and the type of Gilman reagent. Electron withdrawing groups clearly will facilitate nucleophilic attack and favor an unsymmetrical transition state. The adduct in which R and metal have been added cis to the triple bond must be produced from the initial bridged structure by a reorganization, the elements of which are well precedented.

Finally, Fig. 2(c) shows the orbital interactions between d (Cu) and ψ_3^* of an enone which could lead to conjugate (β) addition of nucleophilic copper (and eventually carbon). It is also clear that a similar bonding arrangement can be written for 1,2-carbonyl addition to an enone, which raises the question as to why 1,4-addition is so heavily favored. Two relevant factors would appear to be: (1) greater electron deficiency at C_β relative to C (carbonyl) and (2) a disfavoring of 1,2-addition by "α-effect" repulsion between the three lone electron pairs on oxygen and the d lone pairs on copper in the 1,2-carbonyl adduct, $R_2C\begin{smallmatrix}\diagup O^- \\ \diagdown CuR_2\end{smallmatrix}$. It is also possible that the enone-cuprate reaction proceeds via a single electron transfer pathway followed by coupling of copper to the center of highest spin density rather than by β-addition of nucleophilic copper. This long-standing mechanistic question[14] still remains to be settled.[15]

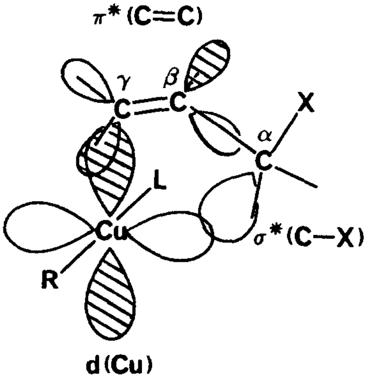
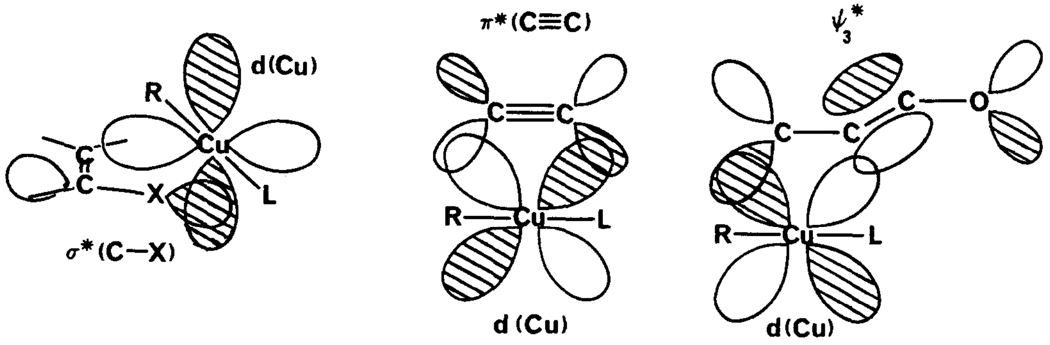


FIGURE 1



coupling to C_{sp^2}-X

(a)

addition to C≡C

(b)

addition to enone

(c)

FIGURE 2

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15. This research was assisted financially by a grant from the National Science Foundation.

(Received in USA 13 April 1984)