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A POSSIBLE TRANSITION STATE ASSEMBLY FOR HIGHLY DIASTEREOSELECTIVE CONJUGATE ADDITION REACTIONS OF LITHIUM DIMETHYLCUPRATE WITH α,β-ENONES

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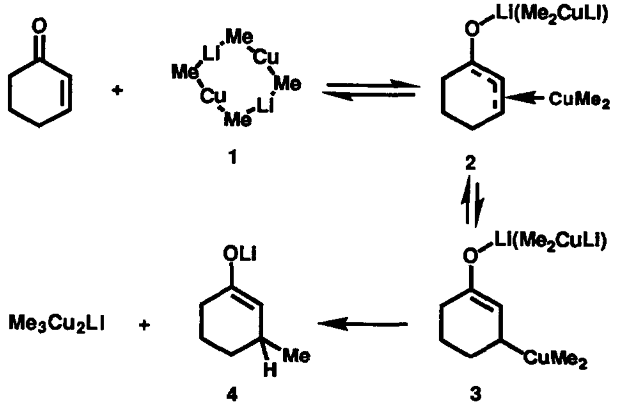
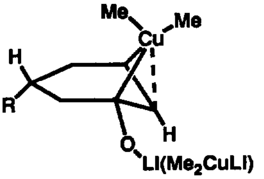
Summary: A transition state assembly is proposed for the 1,4-addition of lithium dimethylcuprate to α,β-unsaturated ketones which provides general agreement with experimental observations of high stereoselectivity for substrates such as chiral α'-substituted α,β-enones, 5-substituted 2-cyclohexenones, medium ring α,β-enones, and $\Delta^{1,9}$-octalin-2-ones.

The conjugate addition of organocopper (Gilman) reagents to α,β-enones is an important synthetic method[1] whose further development would be greatly enhanced by a deeper mechanistic understanding. Especially critical is a knowledge of the type of pathway which is followed in a particular case, specifically electron transfer via enone radical anions[2] or nucleophilic d,π*-complexation,[3] and the structural nature of the transition state assembly. Unfortunately, progress in this area has been slow because of a number of complicating factors, including: (1) the large variety of possible cuprate reagents with regard to structure, stoichiometry and aggregation, (2) the paucity of structural data on these reagents,[4] and (3) uncertainty as to the most reactive species in solution. The clarifications made thus far in this difficult area have been the result of kinetic, NMR and stereochemical studies.[3] In addition strong evidence has been provided for coordination of the enone carbonyl with a metal such as lithium or magnesium in the transition state assembly.[3a,3b,5,6] The reaction of simple unhindered ketones such as 2-cyclohexenone with the reagent $(Me_2CuLi)_2$ (**1**) can reasonably be formulated to involve a d,π*-complex (**2**)[3] and an enone-copper (III) β-adduct (**3**) as follows. Based on this model it is possible to analyze the stereochemistry of reactions of



lithium dimethylcuprate with enones which show high stereoselectivity to obtain structural evidence for the transition state assembly, assuming a transition state somewhere between structures **2** and **3**. We have proposed in an earlier paper that the highly selective formation of *trans*-3,5-disubstituted cyclohexanones[7] from the reaction of 5-alkyl-2-cyclohexenones with, for example, lithium dimethylcuprate in ether can be understood in terms of a strong preference for transition state assembly **5** over **6**. (The solid and dotted lines to copper in structures **5**, **6** etc. are intended to depict a trihapto coordination geometry for the transition state assembly rather than specific bond orders or bonding arrangements. One possibility for such trihapto coordination is a d(Cu) - π_3*(enone) interaction[3c] involving a d electron pair donated by copper). Using such a model for the transition state assembly, it was possible to devise acyclic α,β-enones which combine with organocuprates with high acyclic 1,4-diastereoselection, for example the following:[3d]



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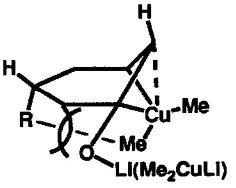

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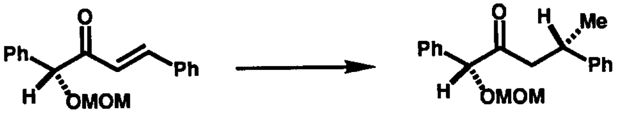
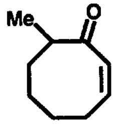


> 30 : 1

The same type of transition state assembly allows a clear-cut explanation of a number of cases of highly diastereoselective reactions of lithium dimethylcuprate with medium-ring α,β-enones[8] which were reported by Still and Galynker who observed high selectivity for formation of *trans* conjugate adducts with enones **7** (> 100 : 1), **8** (96 : 4), **9** (99 : 1), and **10** (96 : 4), and *cis* adduct (94 : 6) from enone **11**. For instance, in the case of enone **7** transition state assembly **12** is clearly more favorable than the alternative **13**, the product from which is not observed.



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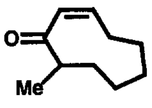

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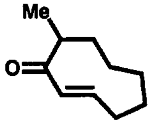

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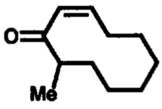

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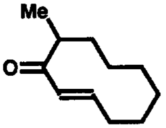

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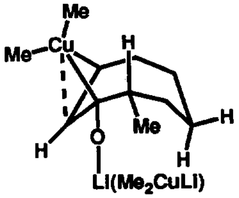

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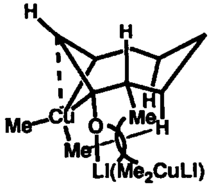

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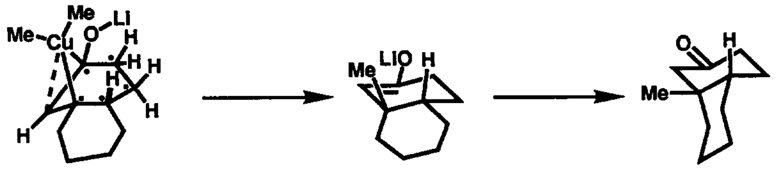
Another important stereoselective enone-cuprate conjugate addition is the reaction of $\Delta^{1,9}$-octalin-2-ones with lithium dimethylcuprate which produces only *cis*-fused adducts in every known instance.[9] This preference is compatible with the model discussed above since transition state assembly **14** leading to *cis*-fused product is less subject to steric repulsions than is structure **15**, a precursor of *trans*-fused adduct. In structures **14** and **15** the dotted atoms are placed in a nearly coplanar arrangement to minimize steric repulsion. Structure **15** is significantly destabilized by a repulsive interaction between the subunits which are starred in **15**. Indeed, repulsion involving the angular Me_2Cu substituent in the Cu(III) β-adduct from **15** (angular Me_2Cu group axial to *two* rings) would also disfavor formation of *trans*-fused adduct.



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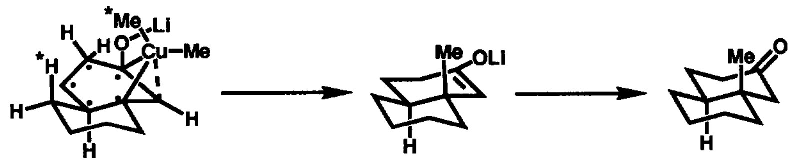

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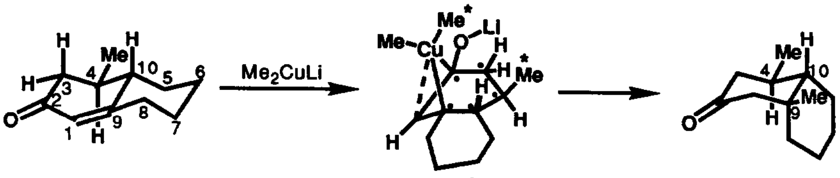
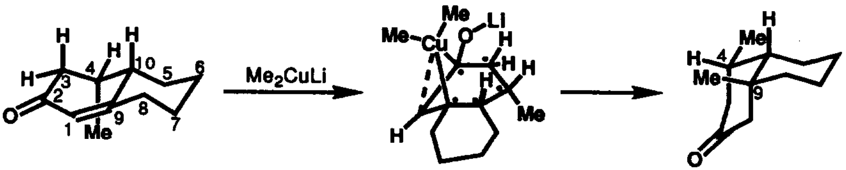
The isomeric 4-methyl substituted $\Delta^{1,9}$-octalin-2-ones **16** and **17** represent interesting test substrates with regard to mechanism, stereochemistry and rate of organocuprate induced conjugate addition. In the case of **16** the 4β-methyl substituent should favor 9α-methylated product (*trans*-fused) in opposition to the usual preference for forming *cis*-fused conjugate adducts in the $\Delta^{1,9}$-octalin-2-one series. Thus, two strong stereochemical preferences are pitted against one another. In contrast, for the diastereomeric enone **17**, *trans*-fused adduct formation is disfavored by both ring-pair and substituent effects. Enones **16** and **17** were synthesized by the method of Stork[10] (ratio 6 : 1 of **16** to **17**) and separated by preparative HPLC (Du Pont Zorbax silica column using 95 : 5 hexane-EtOAc for elution; retention times 16.7 and 17.9 min for **16** and **17**, respectively). Reaction of **16** with lithium dimethylcuprate in ether at -78°C afforded only the *cis*-fused adduct **18**[11] the stereochemistry of which could be assigned by nuclear



16 **16‡** **18**



17 **17‡** **19**

Overhauser effect (NOE) studies.[12] Enone **17** and lithium dimethylcuprate (Et_2O, -78°C) afforded a single product, the *cis*-fused adduct **19** whose stereostructure also followed from a positive NOE between the proton at C-4 and the methyl group at C-9. Competition experiments between enones **16** and **17** showed that the former was less reactive by a factor of at least 20 at -78°C. These results indicate that for enone **16** the bias favoring *trans*-3,5-disubstituted cyclohexanone formation from a 5-methyl-2-cyclohexen-1-one can be overridden by the preference for *cis*-fused adduct formation from a $\Delta^{1,9}$-octalin-2-one derivative and that the opposition of these preferences causes a marked decrease in reactivity of **16**.

The origin of stereoselectivity and rate differences for enones **16** and **17** is unclear for mechanisms such as electron transfer to the enone with subsequent methyl transfer to the radical anion or 1,2-addition of nucleophilic copper to carbonyl followed by rapid rearrangement of methyl to the angular position. However, the rate of difference is understandable on the basis of transition state assemblies **16**‡ and **17**‡ shown above. The free energy of **16**‡ is raised relative to **17**‡ by repulsion between the starred groups of **16**‡ and there is also some relief of steric strain due to the axial methyl in **17** as it approaches transition state **17**‡.

The transition state models described above represent a useful working hypothesis both for further mechanistic/stereochemical studies and for the development of new synthetic applications of the dimethylcuprate-enone reaction. Although the transition state assembly outlined herein for the reagent $(Me_2CuLi)_2$ may apply to other di-*n*-alkylcuprates, it probably cannot be extended to *sec*- or *tert*-alkyl-containing reagents.[13]

References and Notes

1. See G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*, Wiley-Interscience, New York, 1980.
2. See (a) H. O. House and J. M. Wilkins, *J. Org. Chem.*, **43**, 2443 (1978); and (b) H. O. House, *Acc. Chem. Res.* **9**, 59 (1976).
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9. See G. Posner, *Organic Reactions*, **19**, 1 (1972).
10. G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 216 (1963).
11. See J. Marshall and R. A. Ruden, *J. Org. Chem.*, **37**, 659 (1972), who reported the formation of a single adduct from **16**, assumed to be **18**.
12. No NOE effect was observed between the methyl group at C-9 and the methine proton on C-4, and a positive NOE was observed between the proton on C-10 and the methyl group on C-9.
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