

A MECHANISTIC STUDY OF ORGANOCOPPER SUBSTITUTION REACTIONS
WITH SOME ETHYLENIC p-TOLUENESULFONATE ESTERS

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Substitution reactions using organocopper reagents have been used in synthesis of a very wide variety of hydrocarbon structural types¹ and in synthesis of such natural products as fulvoplumierin,² the boll weevil sex attractant,³ insect juvenile hormone,⁴ and various prostaglandins.⁵ The currently most popular mechanism of lithium diorganocuprate(I) coupling with alkyl halides⁶ and tosylates⁷ involves oxidative addition of the electrophile to the copper(I) species which generates a transient copper(III) intermediate; this proposed intermediate then rapidly undergoes reductive elimination of the coupled product (eq 1).⁸ We now report evidence which suggests that at least one alkyl bromide and the corresponding alkyl tosylate react with an organocuprate(I) via different mechanisms; additional evidence suggests that the double bond of certain ethylenic tosylates participates in replacement of the tosyloxy group by the hydrocarbon group derived from the organocuprate(I) reagent (e.g. with retention of configuration at the carbon atom undergoing substitution).

5-Bromo-cis-cyclooctene⁹ seemed a reasonable substrate to probe for the intermediacy of a copper(III) species; it was expected that if a 4-cyclooctenylcopper(III) species were formed, transannular interaction of the double bond with the cyclooctene carbon atom bound to copper might lead to some products having the bicyclo[3.3.0]octane skeleton.¹⁰ Indeed, treating 5-bromo-cis-cyclooctene with excess lithium dimethylcuprate(I) in diethyl ether at 25° produces bicyclo[3.3.0]octanes and cyclooctenes in 70% and 23% yields, respectively (eq 2).¹¹ If a 4-cyclooctenylcopper(III) species is indeed the main intermediate in this reaction, then transannular cyclization of this intermediate is faster than reductive elimination. This result would be especially noteworthy because 4-cyclooctenyl radicals have been formed via radical addition to cis,cis-1,5-cyclooctadiene using various reagents, and the ratio of bicyclooctane to cyclooctene products has been taken to reflect the relative rate with which the radical intermediate is trapped internally (bicyclooctane products) or externally (cyclooctene products).^{12,13}

5-Tosyloxy-cis-cyclooctene also reacts with organocuprate(I) reagents in diethyl ether at 25° but the only products observed are cyclooctenes (eq 3). A similar product distribution would be expected if copper(III) intermediate 1 were formed from an alkyl bromide or from the corresponding alkyl tosylate; the predominance of bicyclooctane products in eq 2 and their virtually complete (< 0.5%) absence in eq 3 suggests therefore that the same intermediate is not formed in these two reactions and that they probably proceed via different reaction pathways.

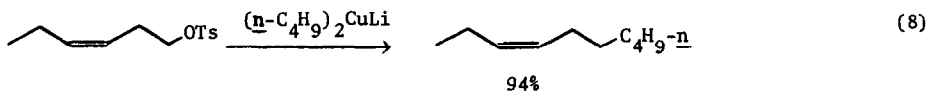
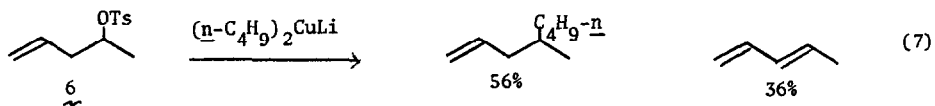
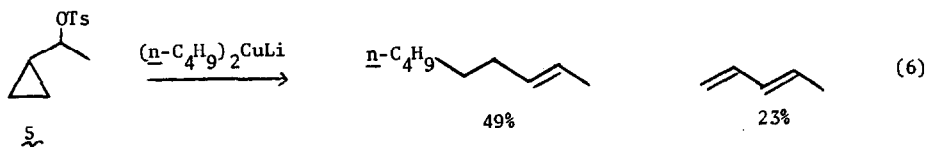
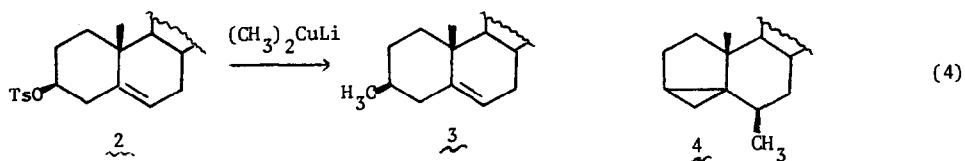
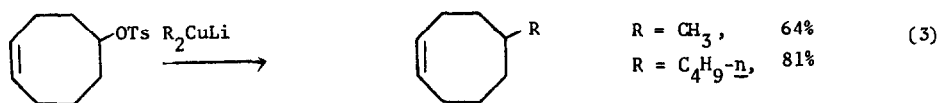
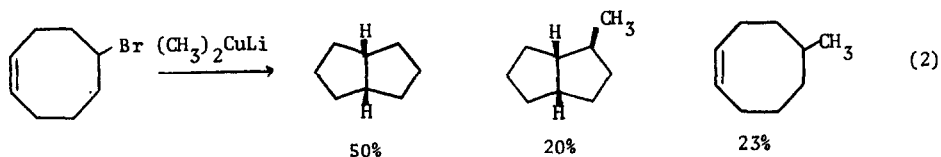
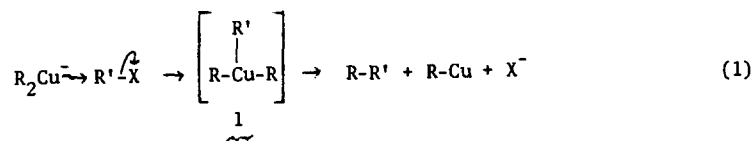
The results summarized in eqs 2 and 3 prompted us to investigate whether the double bond of any ethylenic tosylate would participate in replacement of the tosyloxy group by a hydrocarbon group from an organocuprate(I) reagent. A series of ethylenic tosylates was examined (eqs 4-8). Cholesteryl tosylate (2) reacts with excess lithium dimethylcuprate(I) in diethyl ether at 25° to form 3-β-methyl-5-cholestene (3) and 6-β-methyl-3α,5α-cyclocholestane (4) in approximately equal amounts (80% yield).¹⁴ The stereochemistry of 3β-methylcholestene 3 prepared in this way was established by the identity of its spectral and physical properties with those of 3 prepared via a different, stereochemically unambiguous route starting with 3β-carboxy-5-cholestene.¹⁵ The stereochemistry of 6β-methylcyclocholestane 4 was assigned on the basis of its spectral and physical properties which differed from those of the known 6α-methyl-3α,5α-cyclocholestane.¹⁷ Formation of 3-β-methyl-5-cholestene stereospecifically with retention of configuration at the carbon atom undergoing substitution and formation of the rearranged cyclocholestane stereospecifically with axial methyl attachment at C-6 strongly suggest participation by the 5,6-double bond of cholesteryl tosylate.¹⁸ Although rigorous kinetic data could not be obtained for this reaction, under identical conditions the relative rate of reaction with lithium dimethylcuprate(I) of cholesteryl tosylate and trans-4-tert-butylcyclohexyl tosylate is approximately 3 to 1, which result is also consistent with an increased driving force for reaction of the cholesteryl tosylate.¹⁹

That cyclopropylcarbinyl tosylate 5 undergoes organocopper substitution with rearrangement (eq 6) whereas homoallylic tosylate 6 undergoes direct organocopper substitution (eq 7) is perhaps less surprising when it is noted that cyclopropylcarbinyl systems generally solvolyze faster than the corresponding homoallylic systems.²⁰

Several control experiments were run to investigate whether the substrates in reactions 4 and 5, for example, rearrange prior to reaction with the organocopper reagent. Exposing cholesteryl tosylate (2) to anhydrous lithium iodide in diethyl ether for 24 hr gave no cyclocholestane derivatives, and allowing reaction 5 to run only partially to completion afforded only unrearranged substrate. Thus, at least in these two cases and probably also in reactions 2 and 6, substrate rearrangement occurs during and not prior to reaction with the organocuprate reagent.

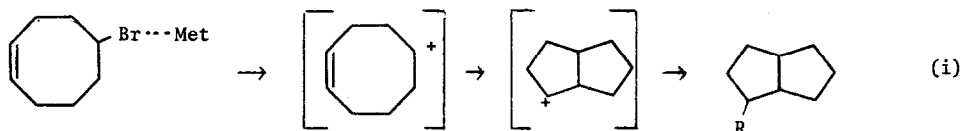
The results in this communication emphasize first that organocopper substitution reactions with alkyl electrophiles probably cannot all be classified as oxidative addition processes involving copper(III) intermediates and emphasize second that the double bond of certain ethylenic tosylates can participate in substitution reactions using nucleophilic organocopper reagents. These results may ultimately be useful in planning organic syntheses which involve organocuprate(I) coupling reactions with unsaturated electrophiles.

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9. This compound was prepared from *cis,cis*-1,5-cyclooctadiene according to the procedure described by A.C. Cope and P.E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959).
10. Bicyclo[3.3.0]octane products need not necessarily be formed only from 4-cyclooctenyl-copper(III) intermediates. They could be formed all or in part via a cationic cyclooctenyl species as in eq i (cf. S.J. Cristol and J.I. Maxwell, *J. Org. Chem.*, manuscript in press).



11. Yields were determined by glpc using calibrated internal standards and are based on electrophilic substrate.
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13. We have found that 5-bromocyclooctene reacts with magnesium metal and then with water to give some bicyclo[3.3.0]octane among other products.
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20. We have found that *exo*-5-norbornenyl tosylate reacts with either methyl lithium or *n*-butyllithium to give *exo*-5-norbornen-2-ol as the major product (67-86% yields) and that *exo*-5-norbornenyl acetate reacts with either dimethyl or di-*n*-butylcopperlithium to give *exo*-5-norbornen-2-ol in 80-85% yields.