

Organocopper Reagent

Reactions of organo copper reagents involve species containing copper-carbon bonds acting as nucleophiles in the presence of organic electrophiles. Organocopper reagents are now commonly used in organic synthesis as mild, selective nucleophiles for substitution and conjugate addition reactions. Since the discovery that copper(I) halides catalyze the conjugate addition of Grignard reagents in 1941, organocopper reagents have emerged as weakly basic, nucleophilic reagents for substitution and addition reactions. The constitution of organocopper compounds depends on their method of preparation and the various kinds of organocopper reagents exhibit different reactivity profiles. As a result, the scope of reactions involving organocopper reagents is extremely broad.

Gilman Reagent:

Gilman first observed that reaction of cuprate salt with 2 equivalent of an organolithium reagent generated an organocuprate (lithium dibutylcuprate, $\text{Bu}_2\text{Cu}_2\text{Li}$). The reagent formed is usually called a Gilman reagent, and its drawn as R_2CuLi .



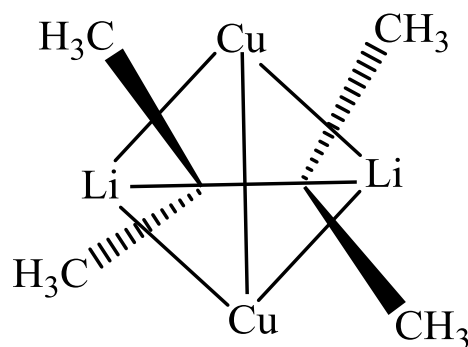
The reaction probably involves an intermediate and conversion of a Cu (I) species to a transient Cu(III) species, and it may proceed via one electron transfer. The stability of such organocopper species varies considerably with their structure. The dimethylcuprate (Me_2CuLi) was stable in ether for hours, at 0°C . Disproportionation is the primary decomposition route of organocuprate. The halide plays a role in stability of the organocuprate. Cuprous iodide gives better results than cuprous bromide.

Properties:

- Organocopper reagents offer a very efficient method for coupling of two different carbon moieties.
- Cu is less electropositive than Li and Mg, the C–Cu bond is less polarized than the C–Li and C–Mg bonds. This difference produces three useful changes in reactivity.
- Organocopper reagents react with alkyl-, alkenyl-, and aryl halides to give alkylated products.
- Organocopper reagents: more selective and can be acylated with acid chlorides without concomitant attack on ketones, alkyl halides, and esters.
- The general reactivity of organocuprates with electrophiles follows the order: $\text{RCOCl} > \text{RCHO} > \text{tosylates, iodides} > \text{epoxides} > \text{bromides} \gg \text{ketones} > \text{esters} > \text{nitriles}$
- In reactions with α,β -unsaturated carbonyl compounds, the organocopper reagents prefer 1,4-addition over 1,2-addition.
- The substitution reaction is promoted by the use of THF or ether-HMPA as a solvent.
- The mechanism of these reactions probably involves a one electron transfer, although other mechanistic approaches are in literature.

Structure:

The compound is often represented as four methyl groups attached to a tetrahedral cluster of lithium and copper atoms. However, in the presence of LiI, the compound seems to be a monomer of composition $(\text{CH}_3)_2\text{CuLi}$.

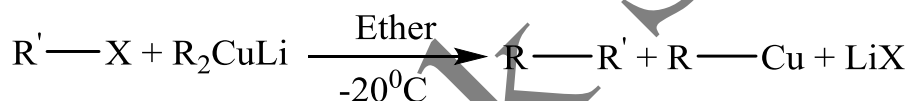


Reactions of Organocuprates:

Substitution reactions

Nucleophilic displacement of halide:

This is best method for the synthesis of alkane and other hydrocarbons from organic halides.



In this reaction R'-X may be methyl halide, primary alkyl halide, 2° alkyl halide, cycloalkyl halide, vinyl halide, allyl halide, propargyl halide.

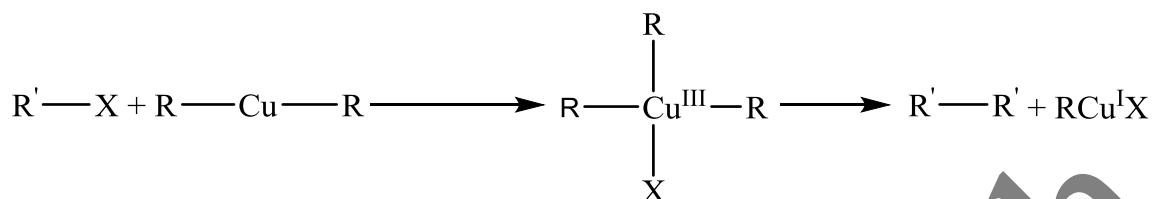
The R of R₂CuLi may also be primary, secondary or tertiary alkyl group but the best result is obtained when R is methyl group. R may be also vinyl, allyl, phenyl and benzyl group.

Mechanism:

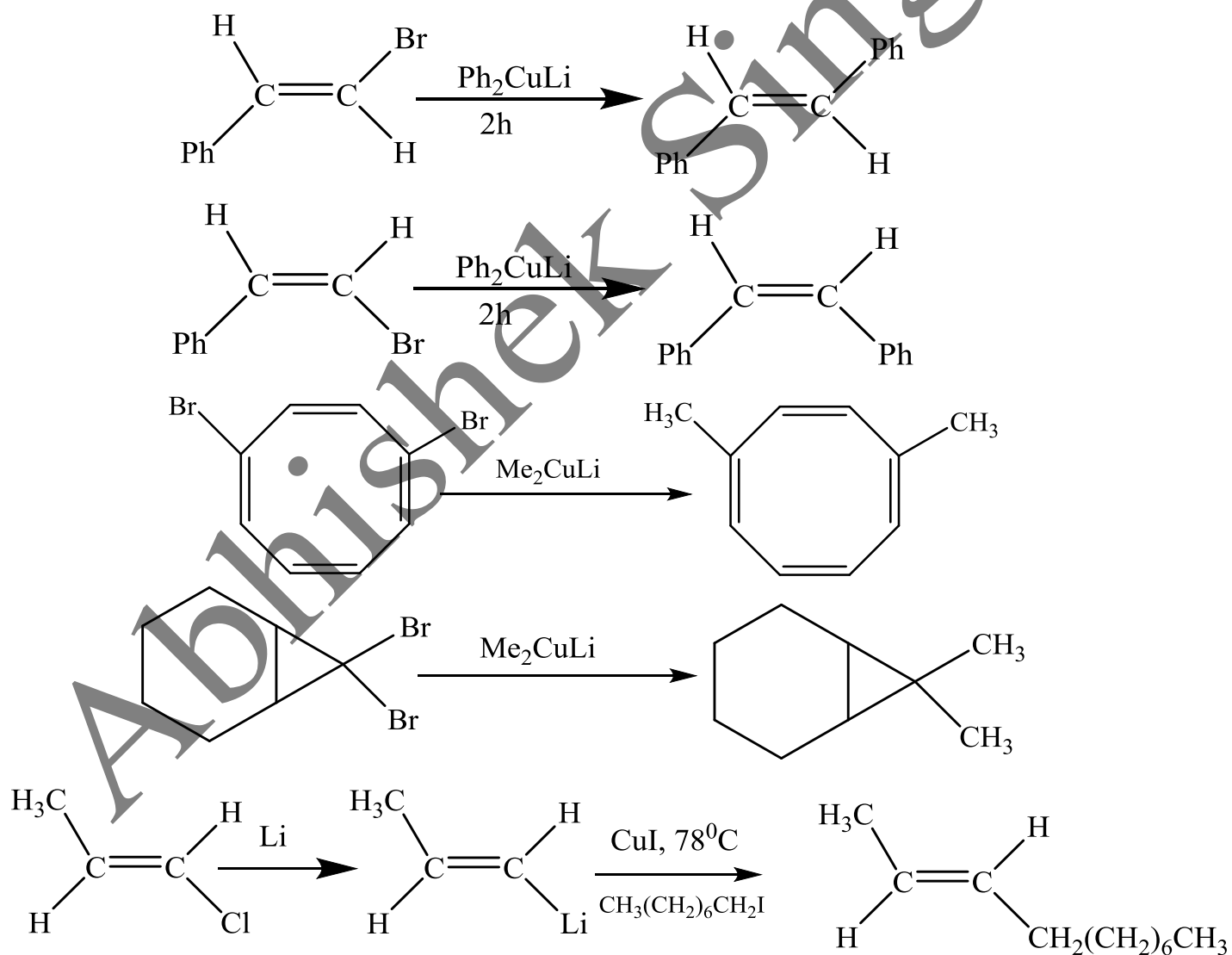
Alkyl and alkenyl halide are reactive, even though the direct displacement mechanism is not feasible, for these halides, the overall mechanism probably consists of two steps: oxidative addition to the metal, after which the oxidation state of the copper is +III, followed by combination of the two groups from the copper. This process, which is very common in transition metal intermediate, is called reductive elimination.

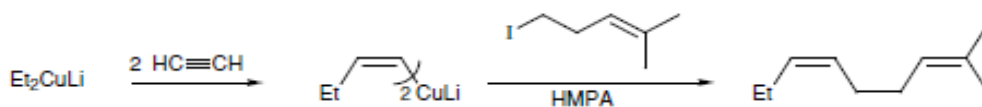
The [R₂Cu]⁻ species is linear and oxidative addition take place perpendicular to this moiety, generating a T shaped structure. The reductive elimination occurs

between adjacent R and R' groups, accounting for the absence of R-R coupling product.

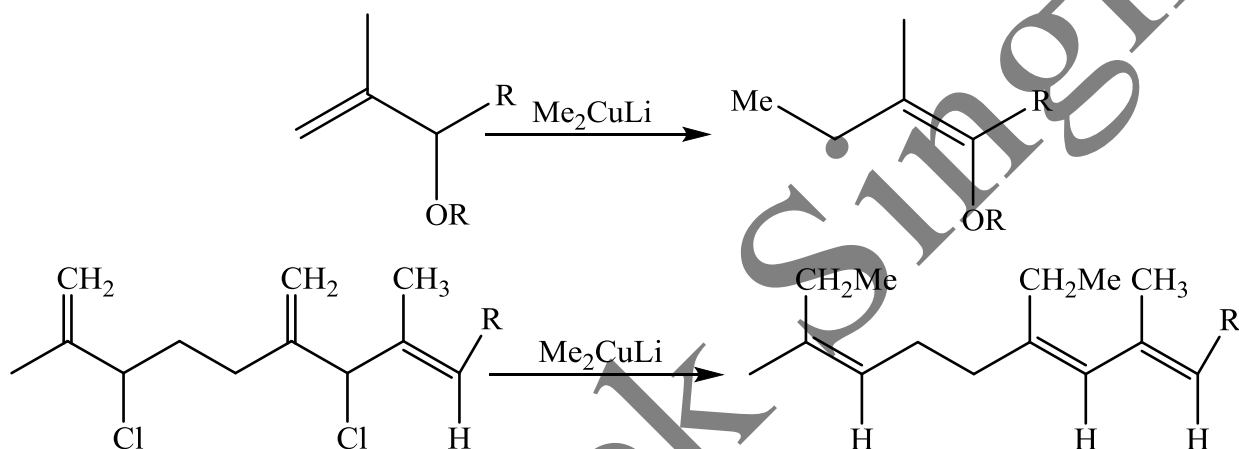


Alkenyl halide coupling reaction proceeds with high stereoselectivity, in contrast to the Grignard and organolithium coupling reactions

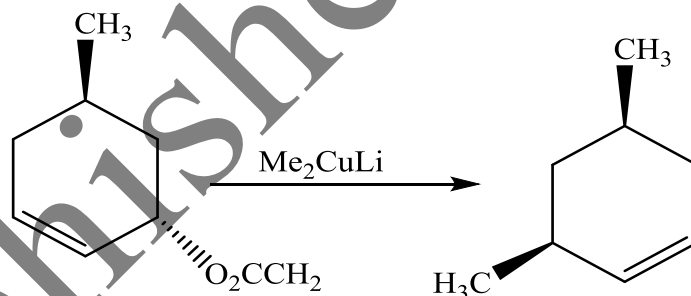




In allylic systems, both α and γ substitution can occur. The reaction conditions can influence the versus γ selectivity.

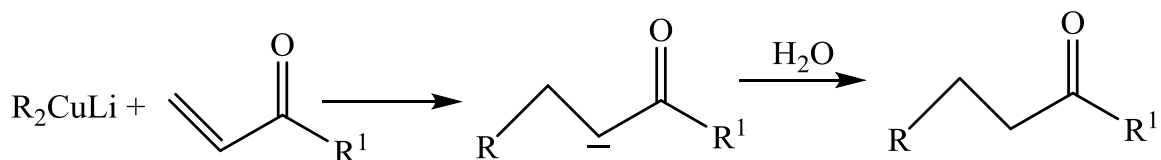


The reaction of cyclic allylic acetate shows a preference for anti stereochemistry.



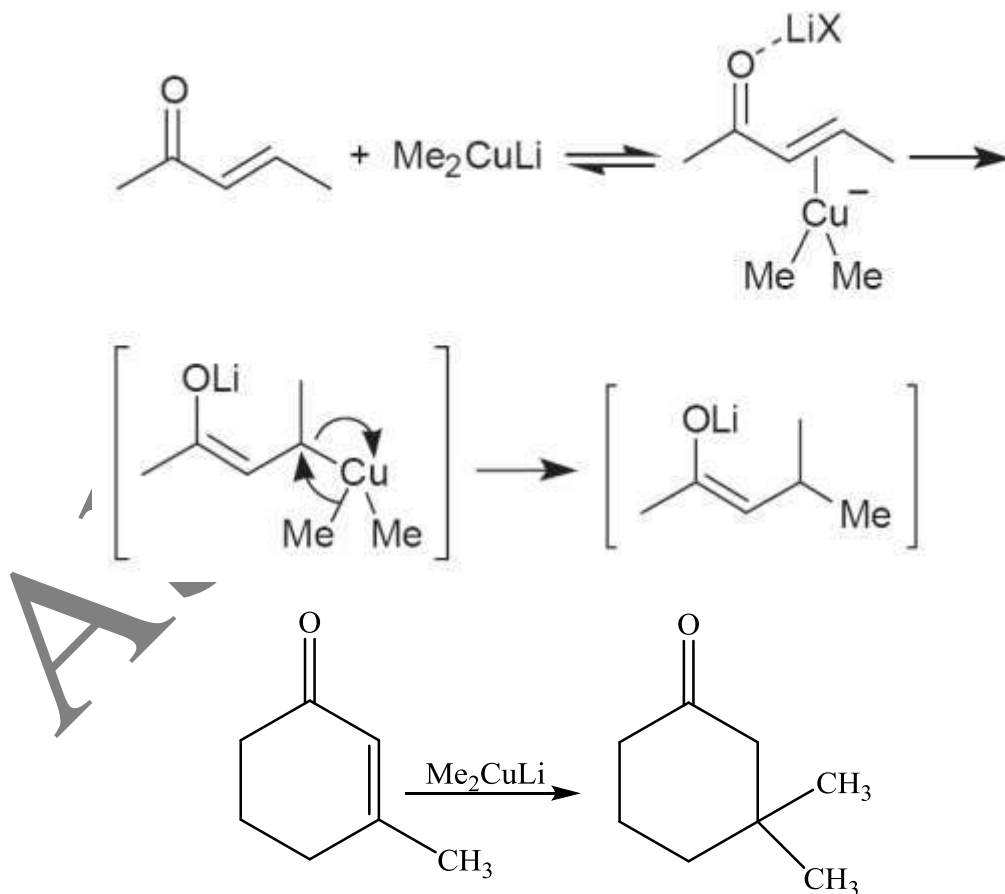
Conjugate Addition:

Organocuprate react with α,β -unsaturated conjugated aldehyde and ketone derivatives to yield almost exclusive 1,4-addition. Initial conjugate addition generates an enolate anion and sequent hydrolysis gives ketone. The reaction is believed to proceed via reductive elimination of a σ -allylcopper (III) compound that leads to a C-C bond.



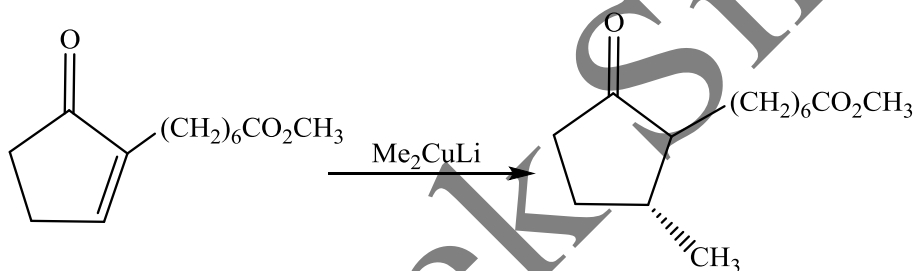
Mechanism:

The mechanism for addition of organocuprates to α,β -unsaturated carbonyl compounds is no less complex than that for substitution reactions. On the basis of current information, conjugate addition of lithiocuprates to α,β -unsaturated ketones and esters may proceed via a initial reversible copper (I)-olefin-lithium association, which then undergoes oxidative addition followed by reductive elimination.

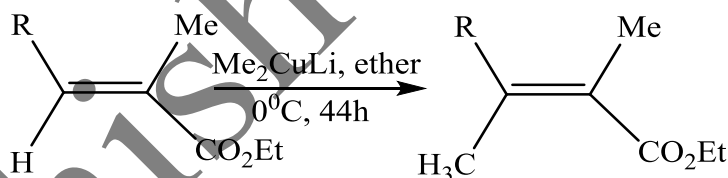


Stereochemistry of 1, 4-addition:

- Factors controlling the stereochemistry of conjugate additions are not well understood.
- Mixtures of isomers are produced, but generally one isomer predominates. Both steric and electronic factors play a role.
- Generally, Michael-type additions have late and hence product like and
- Chair like transition states.
- Example below, for stereo electronic reasons anti parallel attack by the nucleophilic CH_3 is favored over parallel attack.

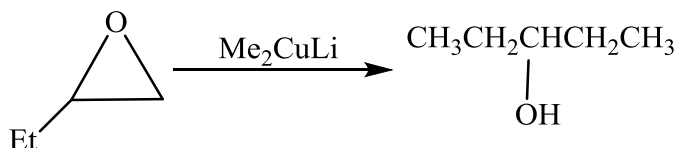


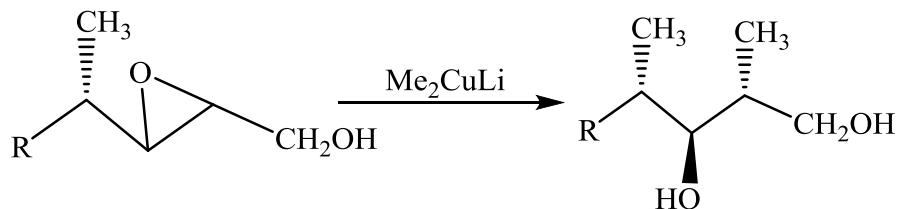
Conjugate esters are less reactive than the corresponding ketones.



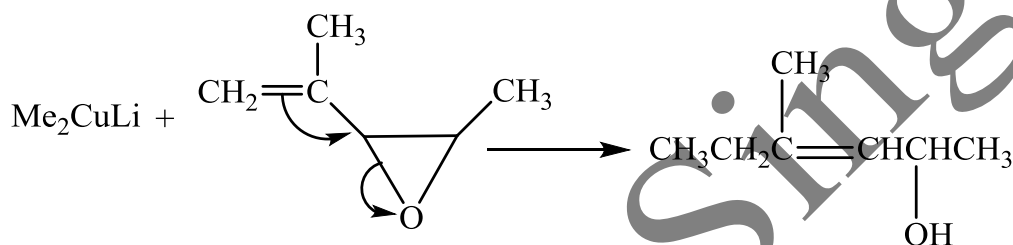
Opening of Epoxides:

Organocopper reagents are excellent nucleophiles for opening of epoxide ring. Saturated epoxides are opened in good yield by lithium dimethylcuprate. Methyl group is introduced at the less hindered carbon of the epoxide ring.



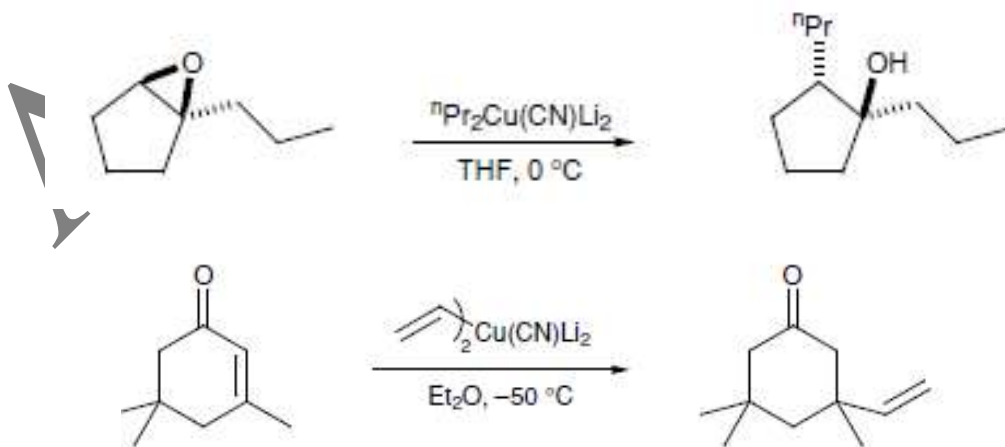
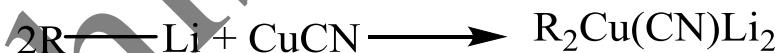


Epoxide with alkenyl substituent undergo alkylation at the double bond with a double bond shift accompanying ring opening, leading to formation of allylic alcohol.



Higher-order organocuprate reagents (Lipshutz reagents):

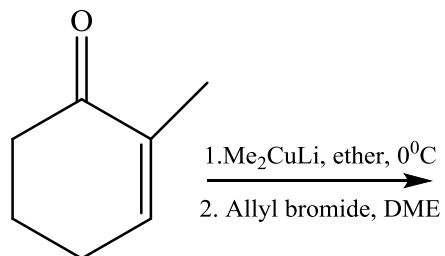
Lipshutz et al developed the so called higher order mixed cuprate, $R_2Cu(CN)Li_2$. It is prepared by reaction of 2 equivalent of an organolithium reagent with cuprous cyanide ($CuCN$). Mixed cuprates react faster than Gilman reagent with alkyl halide, even secondary halides. Mixed organocuprates are generally the choice of purpose. The rate of alkylation was faster than observed with Gilman reagents.



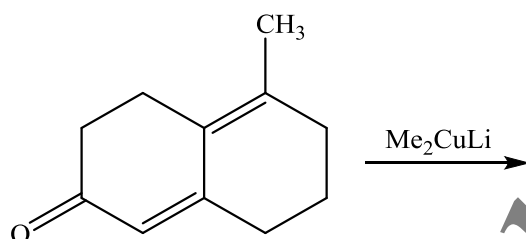
Problems:

1. Predict the major product of following reactions.

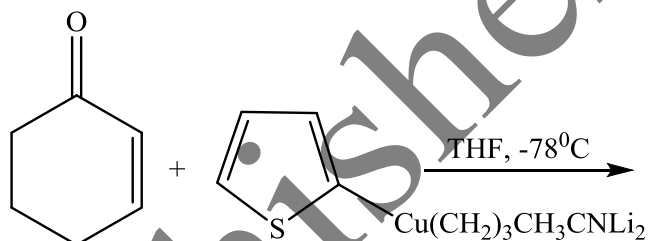
a.



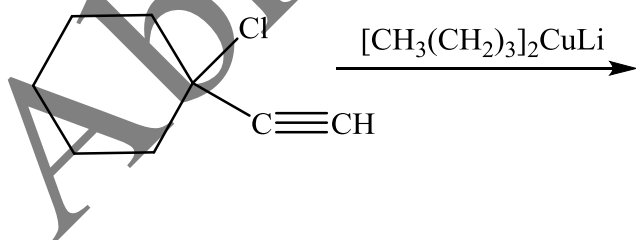
b.



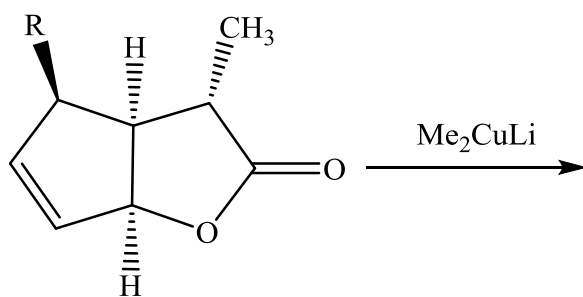
c.



d.



e.



Abhishek Singh