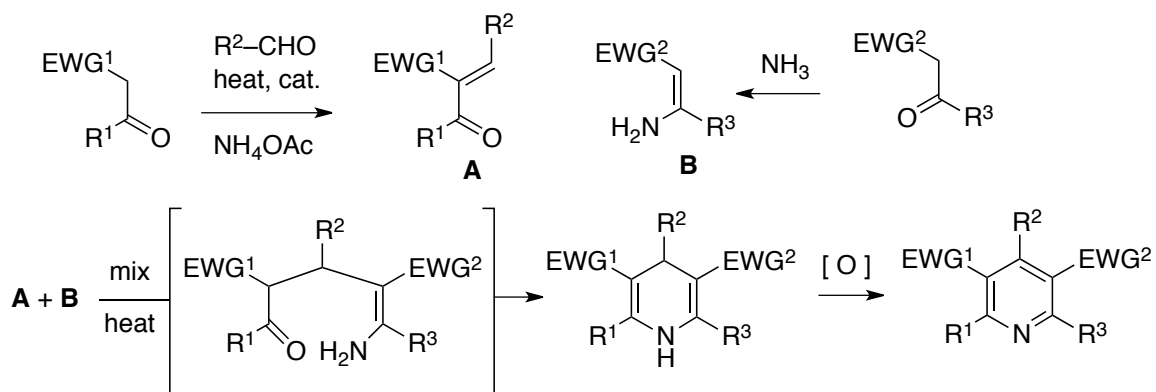


## CHEM 330

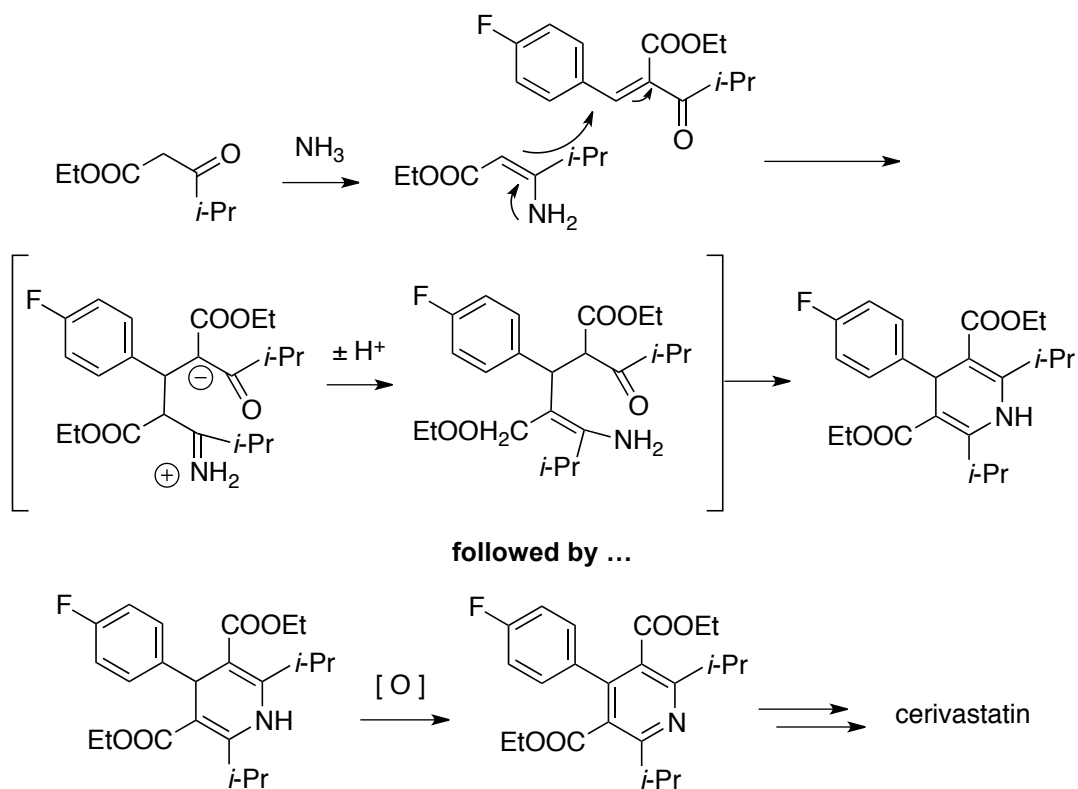
### Topics Discussed on Oct. 30

Description of the pyridine-forming sequence discussed on Oct 28 as the **Hantzsch pyridine synthesis**: an important method for the assembly of pyridines that finds much use in the preparation of pyridine-containing pharmaceuticals

Enamine variant of the Hantzsch pyridine synthesis, demonstrating the use of enamines as Michael donors:



Route to the pyridine unit of cerivastatin by the enamine variant of the Hantzsch synthesis



The problem of conjugate addition of alkyl groups to Michael acceptors

Preferential 1,2-addition (= direct addition to the C=O group) of Grignard and organolithium reagents to Michael acceptors

Principle: the nature of the metal, Mt, bound to the alkyl portion, R, of a generic organometallic agent, R-Mt, modulates the reactivity of R, rendering it more basic, or more nucleophilic, or more inclined to undergo 1,2-addition, or more inclined to undergo 1,4-addition.

Organocopper reagents as reactive agents in 1,4-additions to unsaturated carbonyls

Common oxidation states of copper: Cu(I) and Cu(II)

Oxidizing properties of Cu(II) and consequent non-existence of alkyl-Cu(II) species that are sufficiently long-lived to be useful in organic chemistry

Existence of Cu(I) organometallic species that are stable enough to be used as reagents in synthetic operations

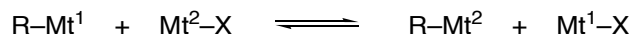
Preparation of organometallics by the "direct" method, e.g.:



Limited scope of the direct method, which works substantially only with metals that are readily oxidized (Li, Mg, Zn, Al ...)

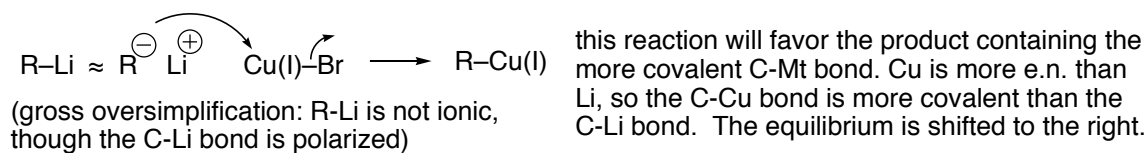
High oxidation potential of Cu(0) and consequent inaccessibility of organocopper agents by the direct method

Transmetallation reaction: exchange of the carbanionic portion between an organometallic agent, R-Mt<sup>1</sup>, and the salt of a second metal, typically a halide Mt<sup>2</sup>X (X = Cl, Br, I):

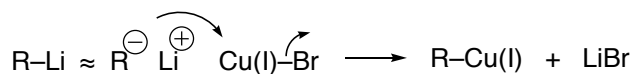


Principle: transmetallation equilibria are strongly shifted toward the organometallic agent containing a more covalent C-Mt bond; i.e., toward the organometallic agent containing the more electronegative metal

Preparation of organocopper reagents by transmetallation, e.g.:

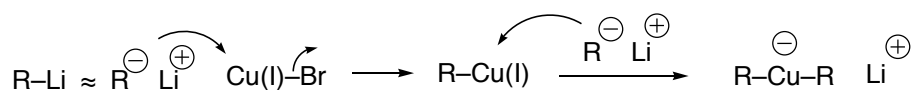


Mono-alkylcopper (I) agents: organometallics of formula R-Cu prepared from 1 mol of R-Li by a transmetallation reaction with 1 mol of Cu(I) halide:



Poor solubility and relative inertness of R-Cu(I) agents

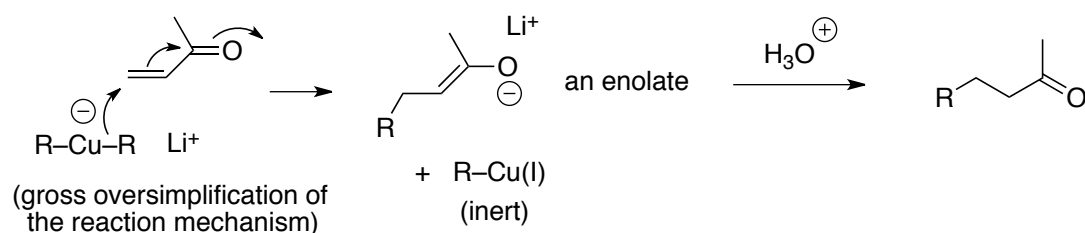
Lithium dialkyl cuprates: copper(I) organometallics of general formula  $\text{R}_2\text{Cu}^- \text{Li}^+$  prepared by reaction of 1 mol of Cu(I) halide plus **two** mols of R-Li, as follows:



Ate complexes: organometallics in which the metal carries a formal negative charge (e.g., borates, aluminates, zincates, cuprates, ...)

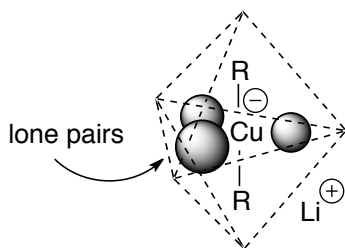
Highly reactive nature of dialkyl cuprates

Strong tendency of the R "carbanion" carried by a cuprate to add in a 1,4 mode to conjugated carbonyls and related species:

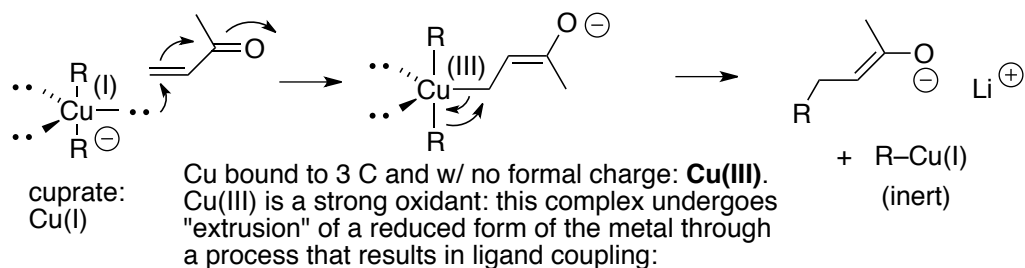


Principle: various mechanistic aspects of organocuprate reactivity remain controversial. What follows constitutes more of a mechanistic model than an actual mechanistic discussion.

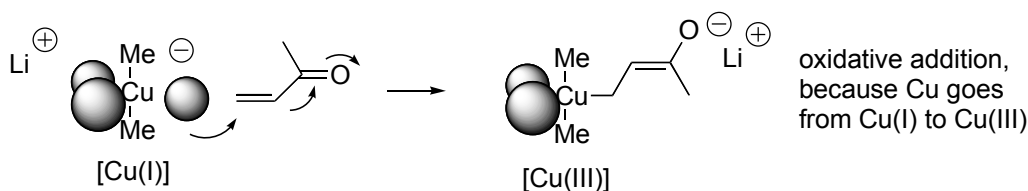
Trigonal bipyramidal structure of a cuprate ion when 3 high-energy lone pairs around the Cu atom are taken into account:



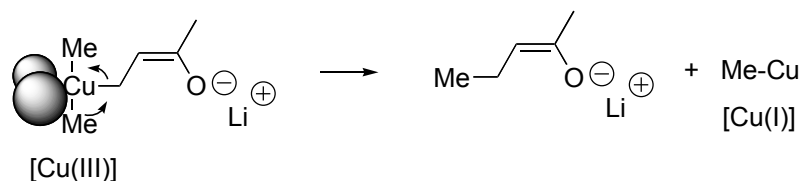
Likely expression of nucleophilic character by the negatively charged Cu atom through one of its three energetic lone pairs:



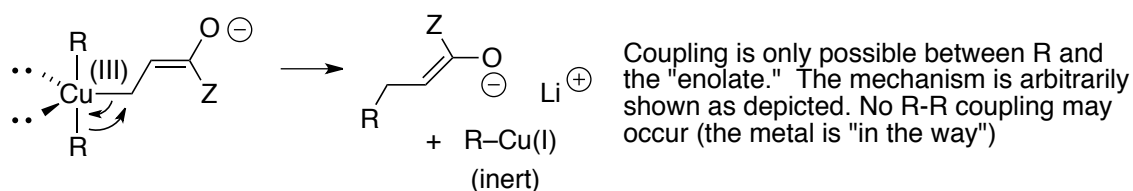
Oxidative addition: a process involving formation of a metal-C bond and proceeding with concomitant 2-electron oxidation of the metal, e.g.:



Reductive elimination: a process involving the decomposition of an organometallic reagent, normally proceeding with ligand coupling, during which the metal undergoes a 2-electron reduction, e.g.:

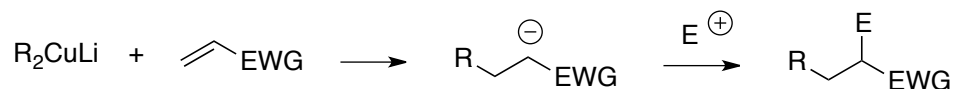


Principle: only *syn*-disposed ligands can undergo coupling during reductive elimination:

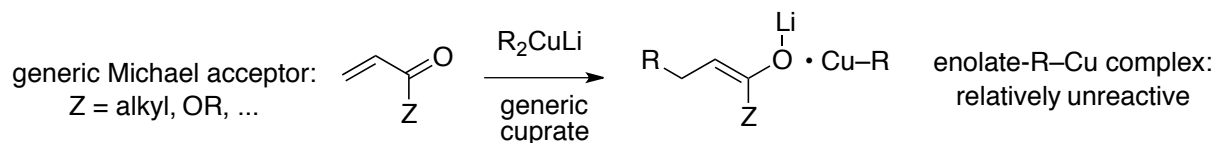


Principle: a dialkyl cuprate transfers **only one** of its two alkyl groups, because of the poor reactivity of simple monoalkyl copper(I) species

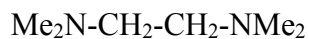
Principle: much like the dissolving metal reductions explored earlier, organocuprate 1,4-additions lead to the formation of carbonyl enolates. Under appropriate conditions, such enolates may be intercepted with suitable electrophiles, leading to the formation of valuable products:



Poor nucleophilic reactivity of enolates generated through cuprate 1,4-additions due to their association with R-Cu(I).



Cu-chelating properties of tetramethylethylenediamine (TMEDA)



Coordination of the monoalkyl-Cu(I) residue with amine ligands (e.g, TMEDA, or even  $Et_3N$ ) as a method to "liberate" the enolate and cause it to react normally with electrophilic agents, e.g.:

