## **CHEM 330**

## **Topics Discussed on Nov. 4**

Mixed cuprates: organometallic agents of formula  $R^1$ –Cu(–)– $R^2$  Mt<sup>+</sup> (Mt = Li, MgBr, etc.) that are prepared as shown below; e.g.:

Relative rate of transfer of alkyl groups connected to the Cu atom in a cuprate:  $sp^2$  alkyls (vinyls, phenyls, etc.) >>  $sp^3$  alkyls (Me, Et, etc.) >> sp alkyls (acetylides)

Methods to suppress the wasteful loss of one of the two alkyl ligands of a cuprate:

• Use of a mixed cuprate carrying a non-transferable "dummy ligand" such as an acetylide (no longer popular these days because of safety issues associated with Cu(I) acetylides):

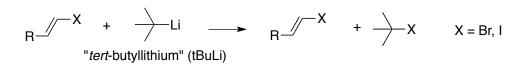
only R is transferable  $n-C_{3}H_{7} \longrightarrow H \xrightarrow{Cul,} n-C_{3}H_{7} \longrightarrow Cu \xrightarrow{R-Li} n-C_{3}H_{7} \longrightarrow Cu-R$ 1-pentyne: a cheap alkyne (relatively inert)  $\downarrow u$   $\downarrow u$  $\downarrow u$ 

• Use of cyanocuprates (widely used in modern synthetic technology):

Cu–CN 
$$\xrightarrow{R-Li}$$
  $\stackrel{\bigcirc}{\longrightarrow}$   $N\equiv C-Cu-R$  Li only R is transferable

• Use of Noyori organocopper agents (widely used; note: these are not "cuprates", because they are not "ate" complexes).

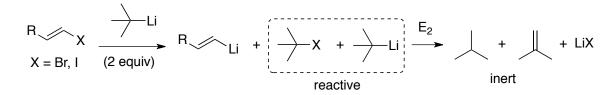
Preparation of organometallics by the halogen-metal exchange reaction, e.g.:



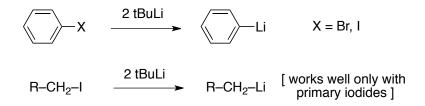
Greater reactivity of tertiary organolithium reagents such as tert-BuLi (pKa  $\approx$  55?) relative to secondary (pKa  $\approx$  52?) or primary (pKa  $\approx$  50) organo-Li species

Driving force for the halogen-metal exchange reaction: decrease in the basicity of the system (pKa sp<sup>3</sup>-Li  $\ge$  50; pKa sp<sup>2</sup>-Li  $\approx$  40) and consequent decrease in free energy

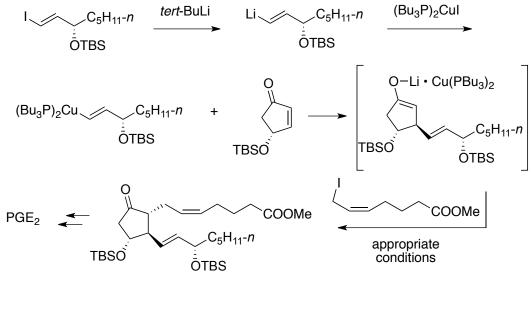
Frequent use of 2 equivalents of tert-BuLi in halogen-metal exchange chemistry, resulting in the ultimate formation of inert isobutene and isobutane; e.g.:



Scope of the halogen-metal exchange reaction: preparation of sp<sup>2</sup> C–Li (all kinds) and primary sp<sup>3</sup> C–Li organometallics:

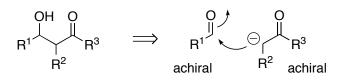


Prostaglandin synthesis via organocopper technology (Noyori – 1985):

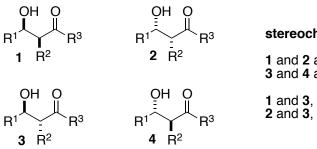


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The problem of assembling 1,3-hydroxycarbonyl compounds by an aldol reaction of an achiral aldehyde with an achiral enolate:



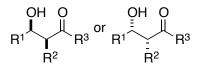
Existence of four stereoisomeric forms of the above 1,3-hydroxycarbonyl compound:

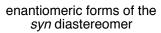


## stereochemical relationships

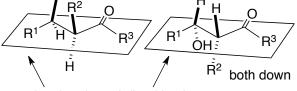
- 1 and 2 are *enantiomers* 3 and 4 are *enantiomers*
- 1 and 3, 1 and 4 are *diastereomers* 2 and 3, 2 and 4 are *diastereomers*

Syn and anti aldol diastereomers:



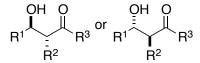


*syn*, because the OH and R<sup>2</sup> groups reside on the same face of the plane defined by the main chain of the molecule in an extended conformation



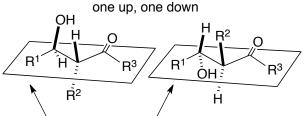
OH both up

molecular plane defined by the main chain in an extended conformation



enantiomeric forms of the anti diastereomer

*anti*, because the OH and R<sup>2</sup> groups reside on opposite faces of the plane defined by the main chain of the molecule in an extended conformation



molecular plane defined by the main chain in an extended conformation

Reminder: enatiomers have identical thermodynamic properties diastereomers have distinct thermodynamic properties

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Principle: it is not going to be possible to achieve selective formation of a particular *enantiomer* of the product during the foregoing aldol reaction, because the thermodynamic properties of two enantiomers are identical, but it may be possible to achieve selective formation of a particular *diastereomer* of the product (*syn* or *anti*), because the thermodynamic properties of two diastereomers differ.

The aldol reaction as a potentially diastereoselective, but not enantioselective, process

Principle: good diastereoselectivity in aldol reactions is often observed if:

- (i) the process occurs under kinetic control (= conditions of irreversibility), and
- (ii) the carbonyl enolate contains a strongly oxophilic metal

Oxophilic metals: small, Lewis acidic ions with a strong charge density and orbitals that interact readily with the orbitals of oxygen, e.g.: Li, B, Ti, Zr....

Existence of metal enolates as two possible geometric isomers: *E* and *Z* enolates



**note**: by convention, the O-Mt substituent takes priority over  $R^3$  when defining the geometry of an enolate, and this even if  $R^3$  were of higher Cahn-Ingold-Prelog priority

Principle: *E* and *Z* metal enolates are configurationally stable and do not interconvert, especially if they are generated and maintained at low temperature (-78 °C) and if Mt is strongly oxophilic