Lecture XXVII: Diastereoselectivity in Addition-Rxns   04-08-2020

Addition onto $C=X$ bonds can form a new stereocenter in cases where $X=N$ or O, or even two adjacent stereocenters when $X=C$.

Addition to Alkenes

These can proceed in an anti or syn geometry. Typically stepwise additions will be anti, and those proceeding through a heterogeneous rxn or a cyclic transition state will be syn. Let's look at some examples:
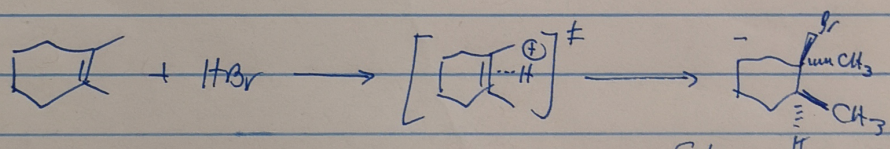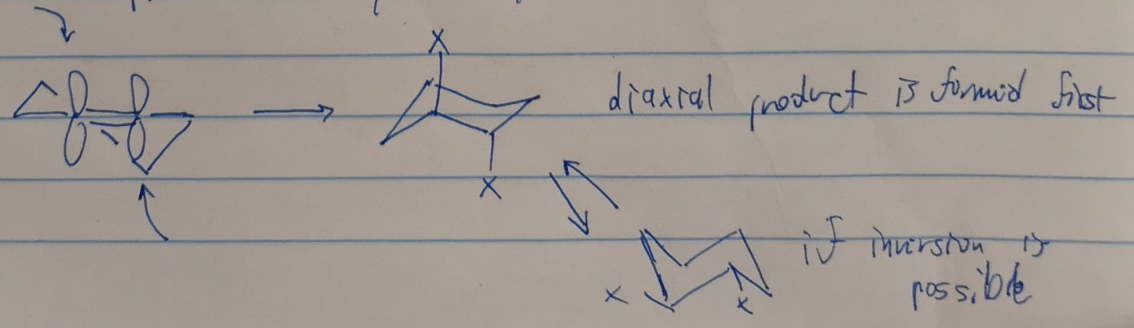

Such a reaction is also regioselective, following Markovnikov's rule: more substituted bromide is produced.
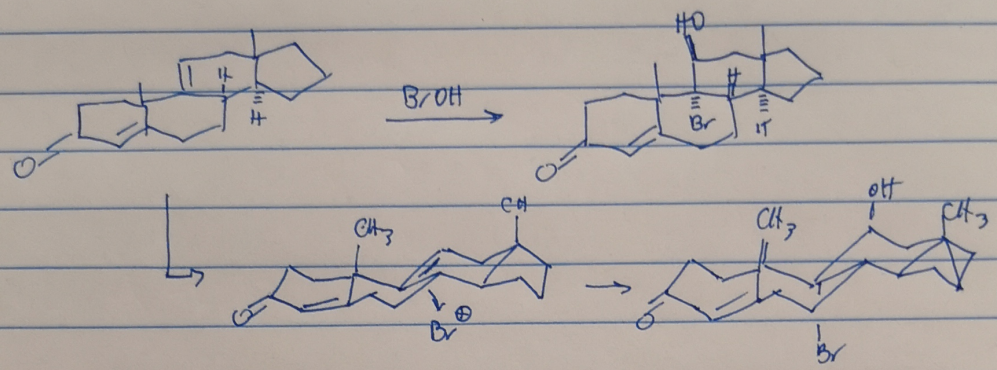
Addition of X_2 proceed through a bromonium cation:
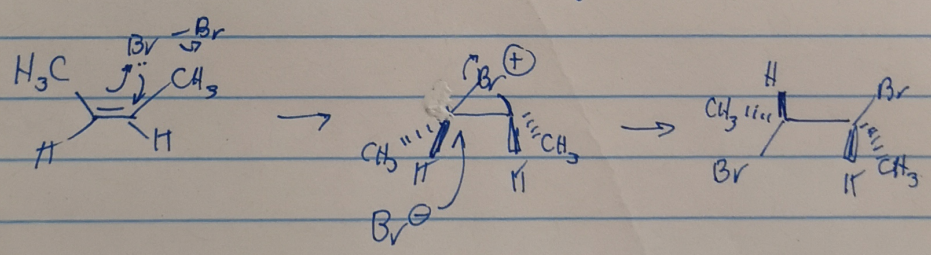
What happens in a cyclic system?

diaxial product is formed first

if inversion is possible

Examples of syn-additions onto the C=C bond include epoxidation, $KMnO_4$ and OsO_4 oxidations, hydroboration and hydrogenation:
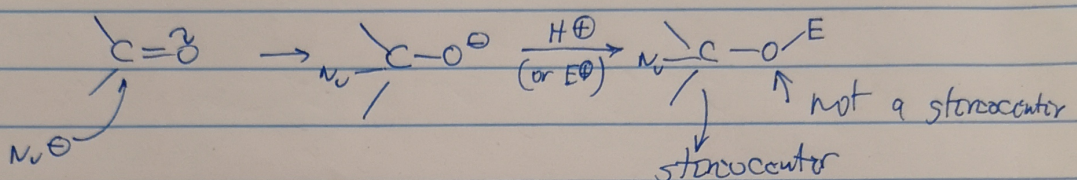
Examples of syn-additions onto the C=C bond include epoxidation, $KMnO_4$ and OsO_4 oxidations, hydroboration and hydrogenation.
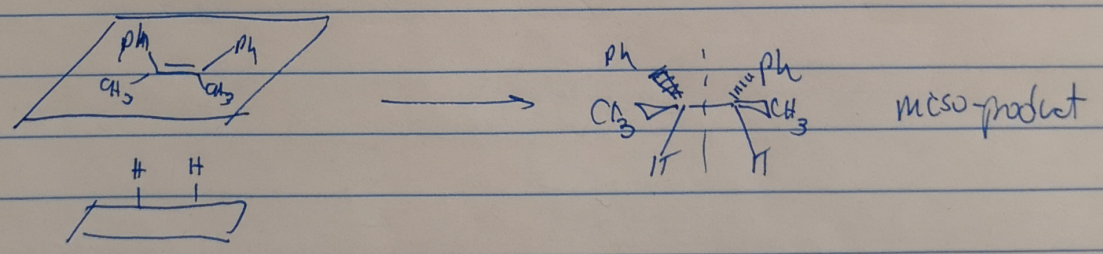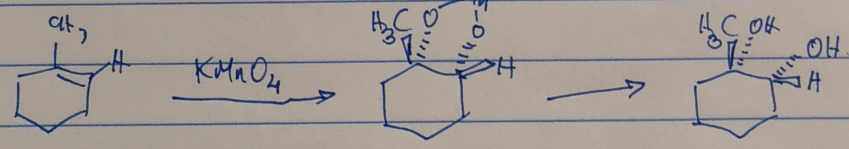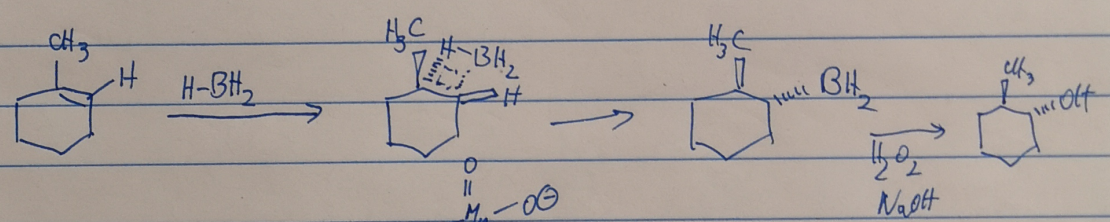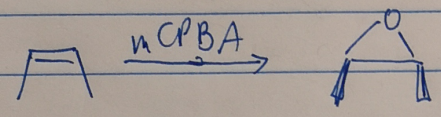
There is a huge body of literature on additions onto C=C bond in enolates, but we will skip it here because it is covered in synthesis classes.
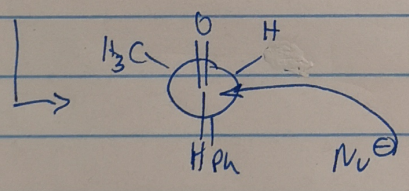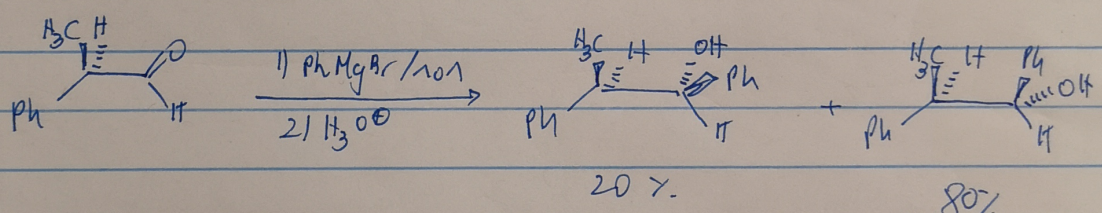
Additions to C=O Bond

$$\underset{\underset{Nu^{\ominus}}{}}{\searrow}C=\overset{..}{\overset{..}{O}} \longrightarrow Nu-\overset{|}{\underset{|}{C}}-O^{\ominus} \xrightarrow[\text{(or } E^{\oplus})]{H^{\oplus}} Nu-\overset{|}{\underset{|}{C}}-O-E$$

↑ not a stereocenter

↓ stereocenter

In the case where C=O group is next to another stereocenter, this addition proceeds diastereoselectively. A great number of models was proposed to explain this diastereoselectivity.

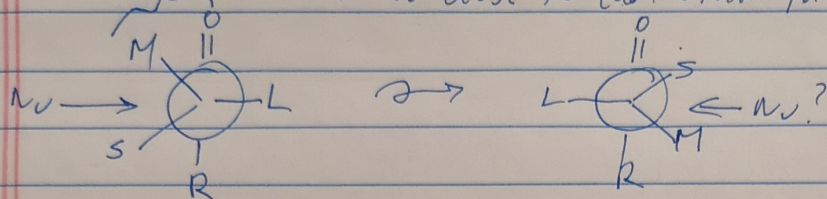## Cram's Rule (1952)

JACS, 1952, 74, 5828.

20 %.   80%

However, this model used an eclipsing conformation to explain selectivity. Felkin (1968, Tet Lett, 1968, 9, 2199) also noticed that in ketones stereoselectivity increases with steric bulk!

Cram   Felkin
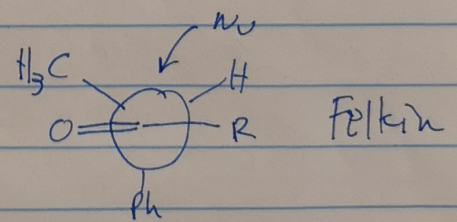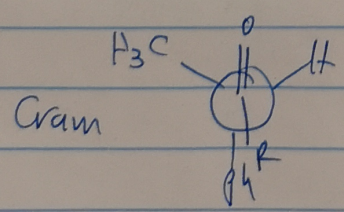
$R = t\text{-}Bu : 98/2$ } inconsistent with Cram's model
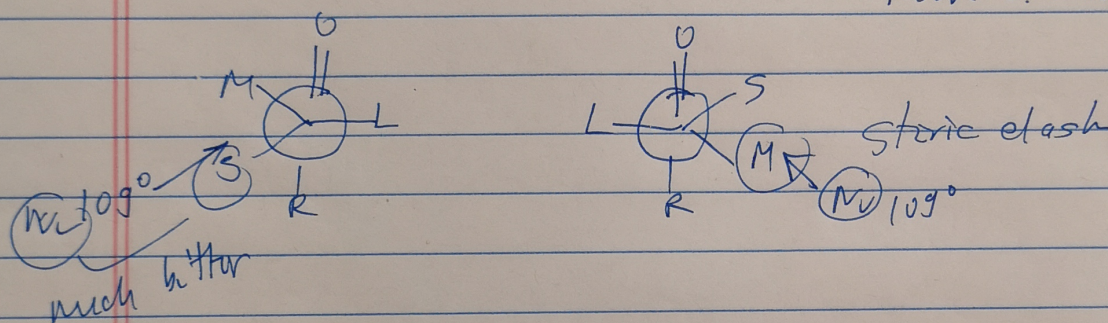$Me : \quad 74/26$

but why would these
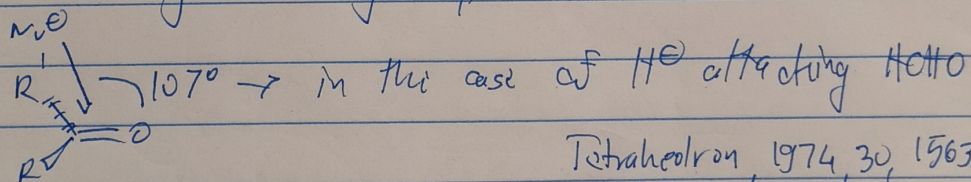two be close to each other in the first place?

Anh corrected the Felkin model by suggesting that
nucleophile attack is not perpendicular, instead proceeding
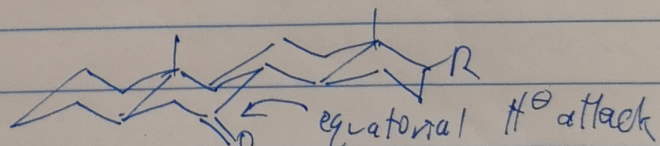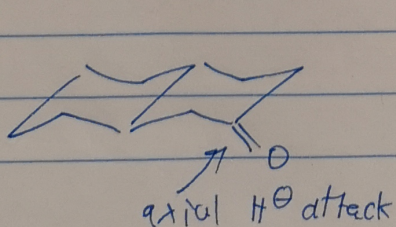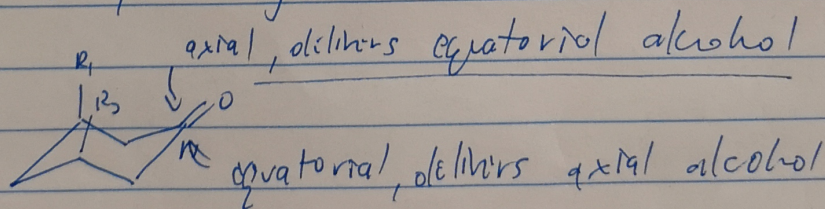at a Bürgi-Dunitz angle of 109°

Nouv. J. Chim. 1977 /61

much better

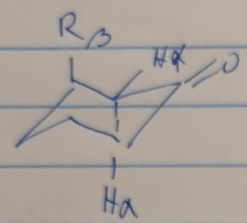Bürgi-Dunitz angle (or trajectory):

107° → in the case of $H^{\ominus}$ attacking HCHO

Tetrahedron, 1974, 30, 1563

In cyclic ketones, axial attack often happens with small organo-
metallic or hydride reagents:

axial, delivers equatorial alcohol

equatorial, delivers axial alcohol

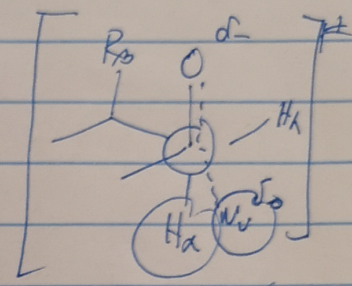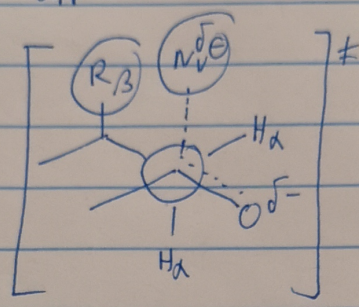equatorial $H^{\ominus}$ attack

axial $H^{\ominus}$ attack

Felkin adapted his model to cyclic ketones:

axial
approach ↓

equatorial
approach ↓

staggered TS

better by default, but gets into
1,3-diaxial strain with larger nucleophiles

eclipsed TS

Those are some of the classical studies in dynamic
stereochemistry. Some of these rules change in cases
of Lewis-acid complexation of carbonyl groups, which
restricts conformational choices.