CHEM 330

Topics Discussed on Nov 10

Aldol reactions of aldehyde enolates

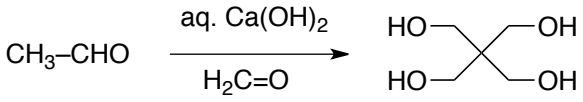
Principle: as a consequence of the difficulties encountered in the deprotonation of aldehydes with, e.g., LDA (rate of deprotonation ≈ rate of aldol addition of the enolate to an intact aldehyde and consequent polymerization of the aldeyde under basic conditions), aldehydes are unsuitable for the conduct of stereocontrolled aldol reactions of the type seen in CHEM 330. Furthermore, lithiated imines, hydrazones, etc. are also generally not useful for the conduct of stereocontrolled aldol reactions

Aldol reactions of aldehydes as processes of industrial significance but of limited scope

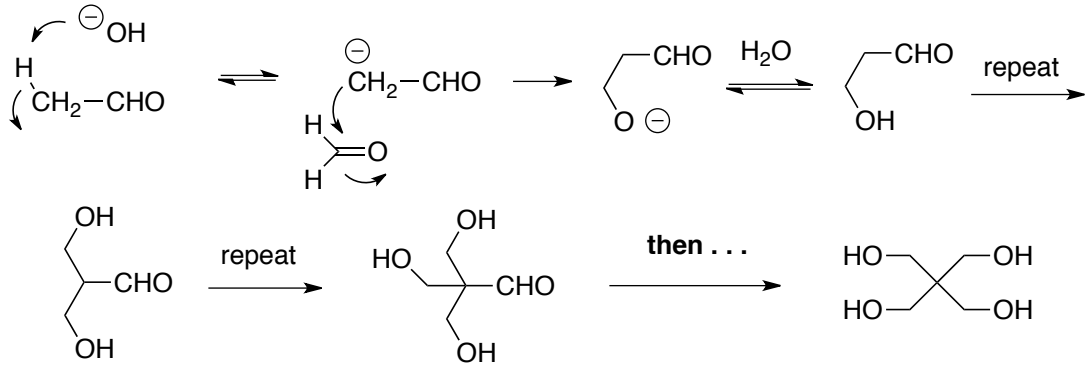
Principle: industrially important aldol reactions are generally carried out by converting the aldehyde *partially* and *reversibly* to the enolate with a weak base, and by intercepting the enolate with appropriate electrophiles in *situ.*

> in that respect, these aldol reactions differ from the ones seen so far in CHEM 330, all of which involve: (i) complete and irreversible conversion of the nucleophilic carbonyl component into the corresponding enolate, and (ii) kinetically controlled addition of said enolate to an aldehyde.

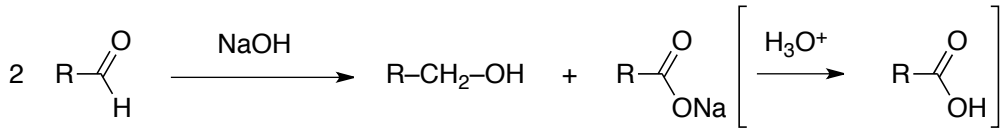
Applications: synthesis of polyols (= poly-alcohols), such as pentaerythritol (structure below), of interest as components of polyester resins used in paints and coatings, as well as in the manufacture of commercial explosives:



Mechanism for the formation of pentaerythritol:

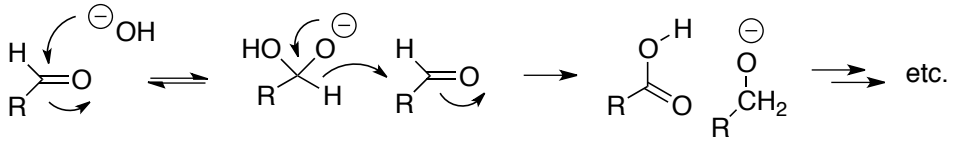


The Cannizzaro reaction: disproportionation of non-enolizable aldehydes, such as HCHO or PhCHO, upon reaction with, e.g., NaOH:

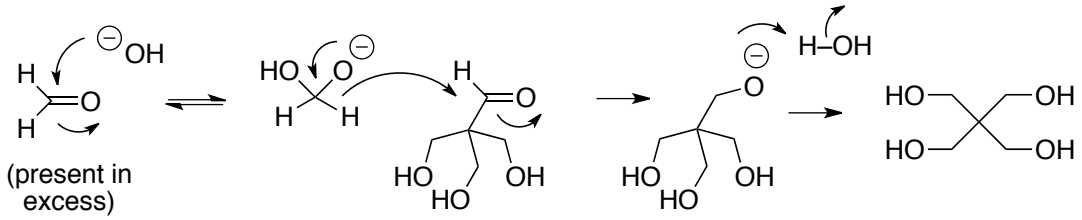


a non enolizable aldehyde

Key step in the mechanism of the Cannizzaro reaction: hydride transfer from a gem-diolate anion to an intact aldehyde:



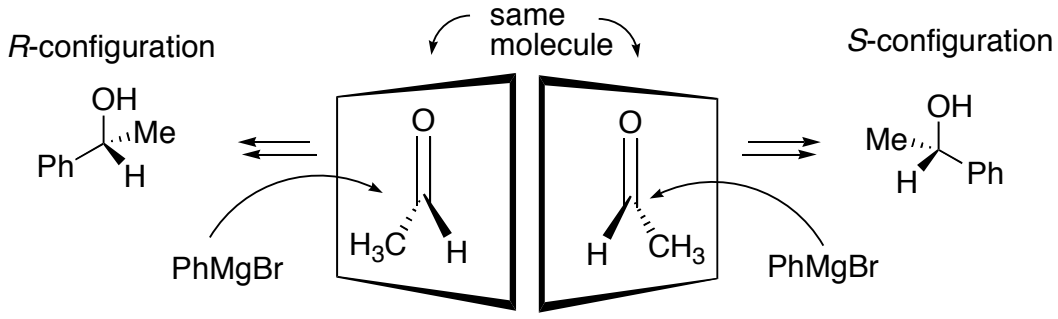
The Cannizzaro step in the industrial synthesis of pentaerythritol:



* * *

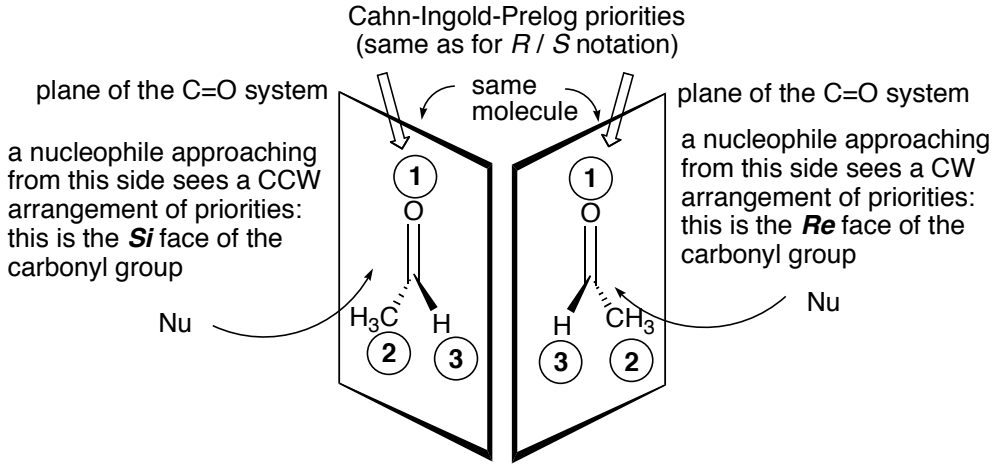
The problem of absolute stereocontrol in aldol reactions

Principle: the configuration, *R* or *S*, of a stereogenic center formed upon the addition of a nucleophile to an aldehyde depends on which face of the C=O group interacts with the incoming nucleophile:



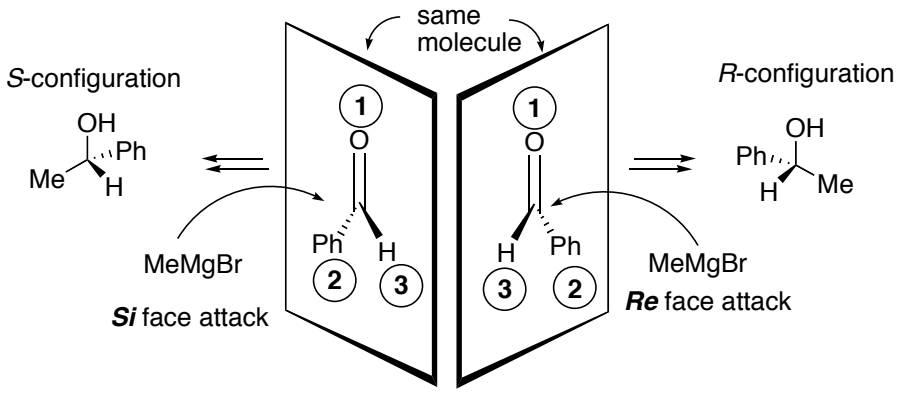
as shown in the above diagram, nucleophilic attack from one face of the C=O group produces one configuration of the newly formed stereogenic center; attack from the opposite face will produce the other configuration.

Si and *Re* stereochemical descriptors to distinguish the 2 faces of a carbonyl group:



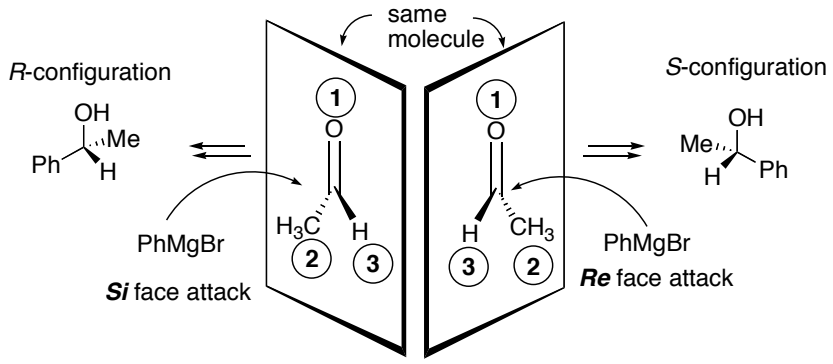
IMPORTANT: attack from the *Re* face does not necessarily lead to the *R* configuration of the newly formed stereogenic carbon. Likewise, attack from the *Si* face does not necessarily produce the *S* configuration. Which configuration is formed depends **both** on which face of the C=O reacts with the incoming Nu, **and** on the priorities of Nu and of the C=O substituents.

Examples:



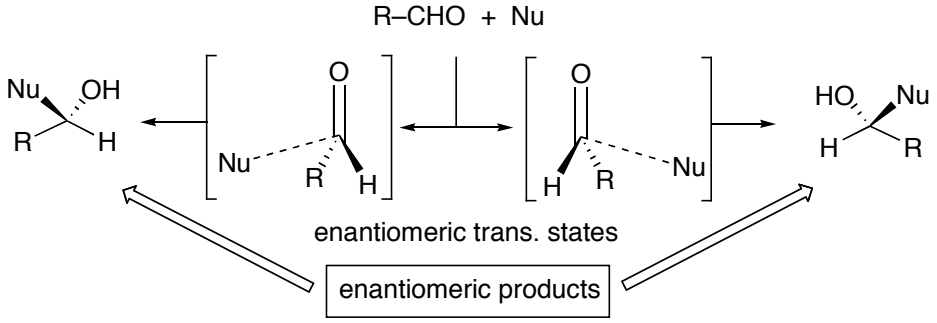
In this case, nucleophilic attack from the *Si* face produces the *S* configuration of the newly formed stereogenic center; *Re* face attack produces the *R* configuration.

BUT:



In this case, nucleophilic attack from the *Si* face produces the *R* configuration of the newly formed stereogenic center; *Re* face attack produces the *S* configuration.

Principle: the transition states for the attack of an achiral nucleophile to either of the two faces of an achiral aldehyde are enantiomeric; therefore, they are thermodynamically equivalent. A reactive system comprising an achiral aldehyde + an achiral nucleophile will evolve with equal probability toward either of the 2 TS's, resulting in formation of a racemic product:



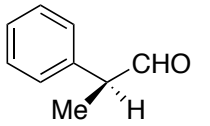
Breaking the mirror-image symmetry of the two possible transition states of the aldol process by introducing chirality in the aldehyde (the substrate of the reaction), in the nucleophile (the reagent), or in both:

> under such conditions, the above transition states become *diastereomeric*; i.e., thermodynamically inequivalent. Therefore, one of them may become favored over the other

Asymmetric reaction: one in which newly created stereogenic centers form selectively with one configuration

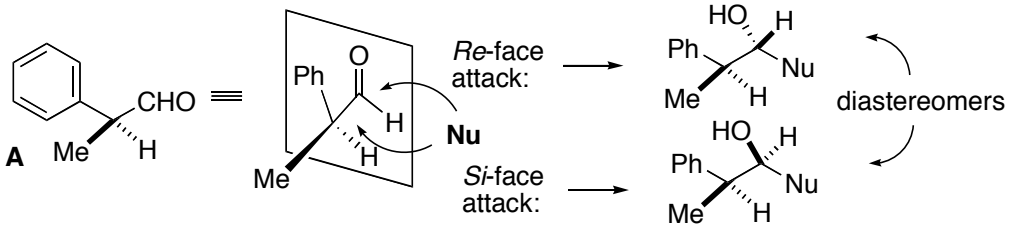
Substrate control (= chirality present in the aldehyde), reagent control (= chirality present in the enolate), double diastereocontrol (= chirality present in both aldehyde and enolate) in asymmetric reactions

Substrate control in nucleophilic additions to carbonyl groups: the case of aldehydes such as the one shown below ("Cram aldehyde," after D. J. Cram), in which a stereogenic center at the α-position of (= closest to) the carbonyl group carries **only H and alkyl** substituents:



[(*S*)-configuration shown]

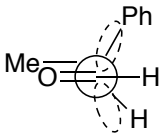
Principle: *a priori*, the above aldehyde may react with a nucleophile, **Nu**, to form either of 2 diastereomeric products, depending on whether **Nu** attacks the *Si* or the *Re* face of the carbonyl group:



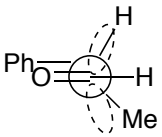
but because the transition states leading to the 2 products are themselves diastereomeric, they are thermodynamically non-equivalent*, so, one of the two products may form diastereoselectively.*

Conformational preferences of (*S*)-Cram aldehyde with respect to internal rotation about the bond between the carbonyl C and the α-C:

O eclipsing smaller Me group: less energetic **more favorable**

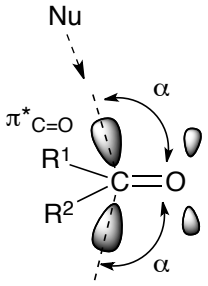


good hyperconj. $\sigma_{C-H} - \pi^*_{C=O}$



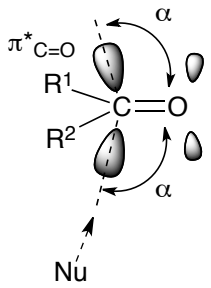
O eclipsing larger Ph group: more energetic **less favorable**

Reaction of the Cram aldehyde with a generic nucleophile: approach to the carbonyl group along a Dunitz-Bürgi trajectory:



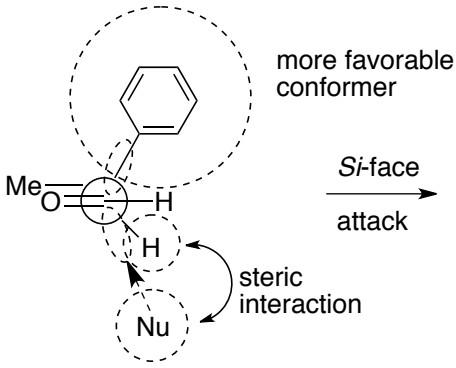
Dunitz-Bürgi angle: α ≈ 107°

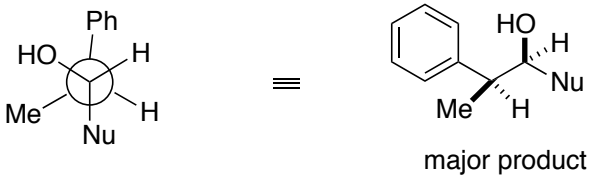
of course, the incoming nucleophile may attack from the top- or the bottom face of the carbonyl group:



Behavior of the (*S*)-aldehyde in question during nucleophilic addition to the C=O system: preferential reaction from the *Si*-face according to the diagram shown below:

this conformation of the aldehyde directs the incoming nucleophile to attack from the *Si* face, because by doing so the Nu experiences the least steric interaction as it "grazes" past the substituent of smallest size (the H in this case) Notice the Dunitz-Bürgi angle of attack (ca. 100° from the C=O axis)

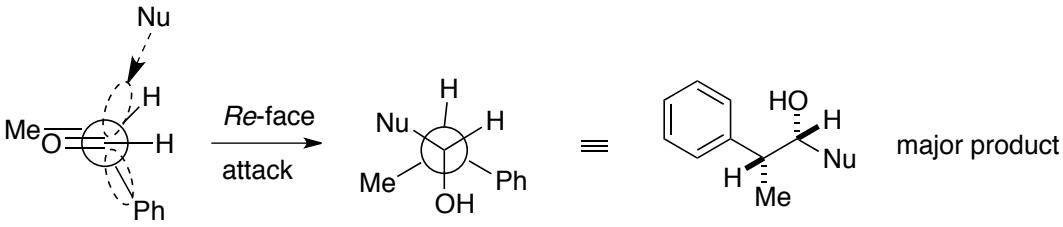




major product

Principle: the chirality present at the α-carbon of the C=O group [(*S*) in this case] promotes preferential reaction from a particular face of the C=O (the *Si* face in the present case)

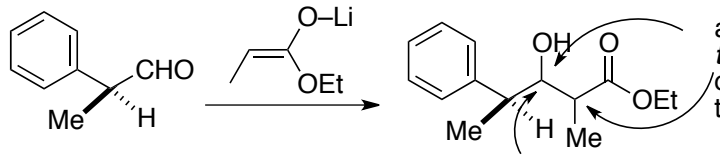
Note: obviously, the (*R*) enantiomer of the Cram aldehyde will tend to react preferentially from the *Re*-face:



Principle: the facial preference of an aldehyde such as the Cram aldehyde, **in which only H or alkyl groups are present at the α-position**, during nucleophilic addition to the C=O group may be rationalized purely on the basis of steric effects

The above rationale for the stereoselectivity observed in the reaction of aldehyde displaying an α-stereogenic carbon bearing **only** C / H substituents as a variant of the **Cram-Felkin** reactivity model (1953), modified to include principles that became known only in the 1970's

Anticipated stereochemical course of the aldol reaction of the above Cram aldehyde of (*S*)-configuration with, e.g., the *E*-enolate of ethyl propionate:



assuming a Zimmermann-Traxler ***topology***, the relative configuration of these centers is determined by the enolate geometry (E / Z)

the abolute configuration of this center is determined by the ***faciality*** of the process; i.e., Cram-Felkin preferences of the substrate, which are controlled by the chirality of the C=O α-center

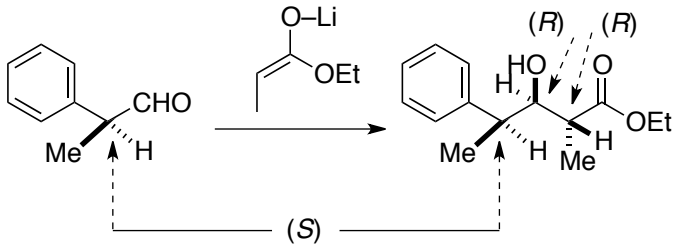
but:

the (*S*)-enantiomer of the Cram aldehyde tends to react with Nu's from the *Si*-face

the *E*-enolate of the ester will add preferentially to the *Si*-face of the aldehyde

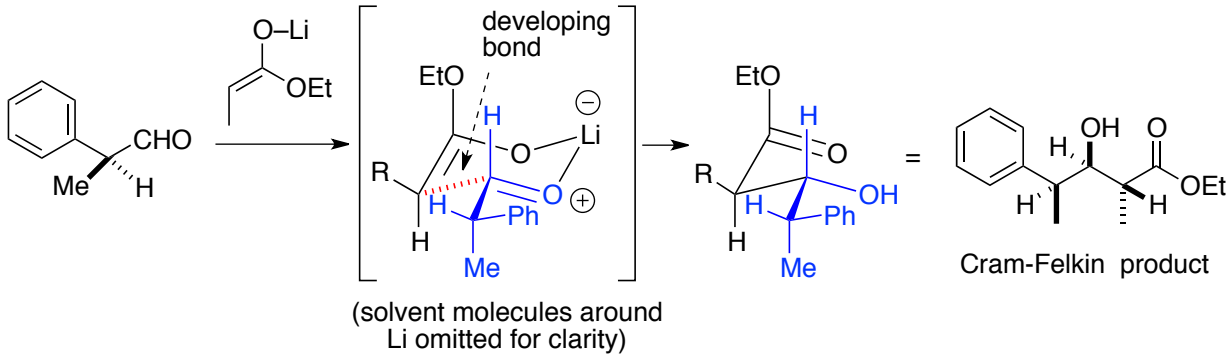
the *E*-enolate of the ester will induce preferential formation of the *anti*-aldol diastereomer

Accordingly, the major product formed in the reaction will be (after the usual aqueous workup):

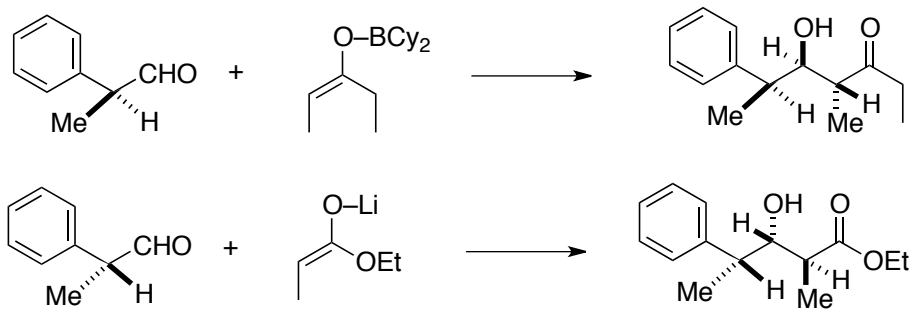


expected (and observed!) major product: the (*S*)-configuration of the Cram aldehyde induces the preferential formation of the new stereogenic centers with the configurations shown

via:



also, e.g.:



Likewise, the major product **expected** (not necessarily **obtained**: more about this later…) during the following representative reactions of *Z*-enolates will be (after the usual aqueous workup):