CHEM60001:
An Introduction to Reaction Stereoelectronics

LECTURE 3 *Stereoelectronics of Transition States – Kinetic vs Thermodynamic Control*

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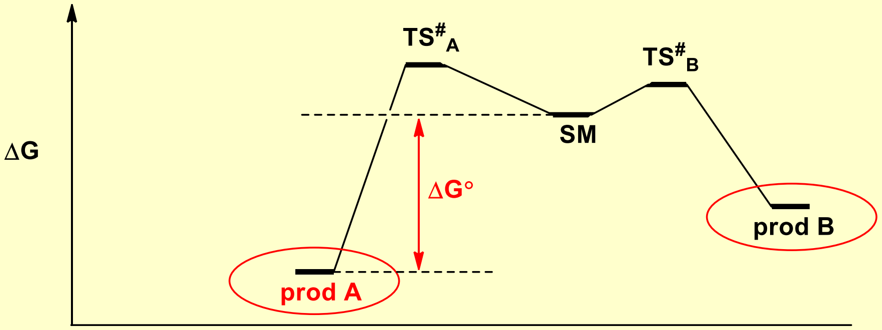
Format & scope of lecture 3

- ***Thermodynamically vs. Kinetically Controlled Reactions***
  - Stereoelectronics of products *vs.* transition states
  - Thermodynamic control: Ley spiroacetal formation
  - Kinetic control: 1,2-diaxial processes
- ***Steric/Strain vs. Stereoelectronic Control of Reactivity***
  - Affect of 1,3-diaxial compression on reactivity
- ***Ring-closure Reactions***
  - Baldwin’s rules
  - The Thorpe-Ingold Effect

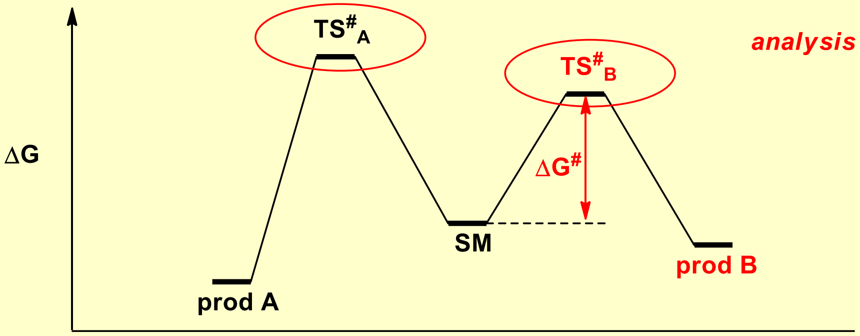
Themodynamic *vs.* kinetic reaction control

- *Thermodynamic control:*
  - the reaction is ***reversible*** under the conditions & so ***equilibrium*** is attained between starting materials & products.
  - the ***most stable product predominates:***



stereoelectronic analysis of PRODUCTS required

- *Kinetic control:*
  - the reaction is ***irreversible*** under the conditions & so the transition state represents a 'point of no return'
  - the ***most rapidly formed product predominates*** (*i.e.* that reached *via* the lowest energy transition state):



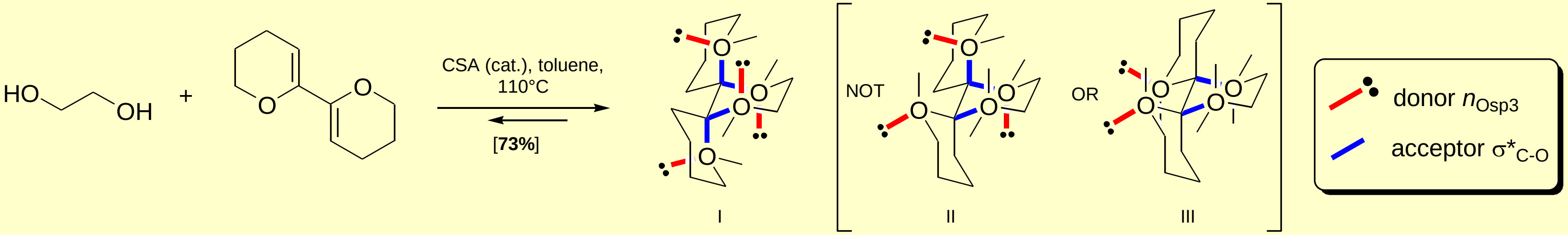
stereoelectronic analysis of TRANSITION STATES required

HAMMOND'S POSTULATE:

the starting material, intermediate or product CLOSEST IN ENERGY to the transition state of interest will be most similar in structure

Thermodynamic control – *e.g. Ley ‘dispoke’ protection*

- *Reaction of **1,2-Diols** with a **bis-enol ether** to give **dispiroketals***
  - The dispiroketal forms as a single diastereomer as the result of its formation being under ***thermodynamic control***. The ***product is stabilised by multiple anomeric effects*** (Deslongchamps theory)

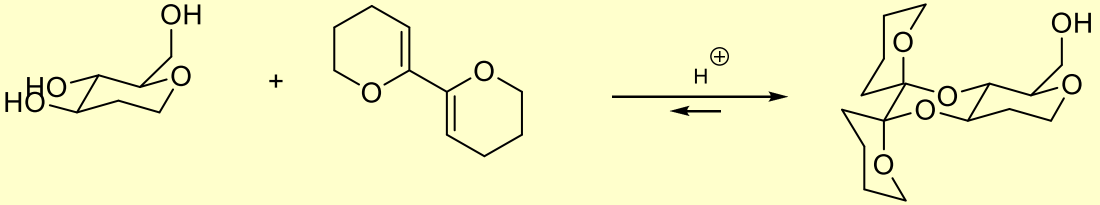


4 anomeric interactions

3 anomeric interactions

2 anomeric interactions

  - used *e.g.* for ***selective protection of di-equatorial 1,2-diols*** (over 1,3-, 1,2-di-axial & 1,2-axial/equatorial diols)

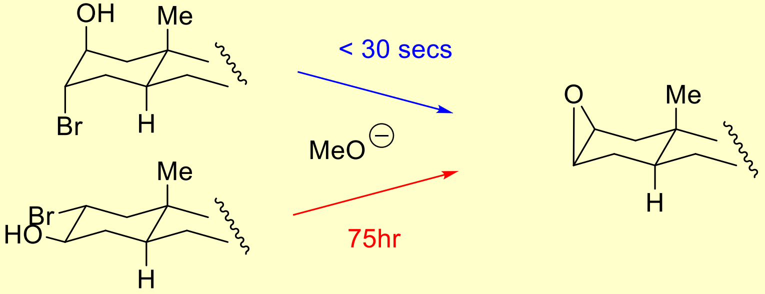


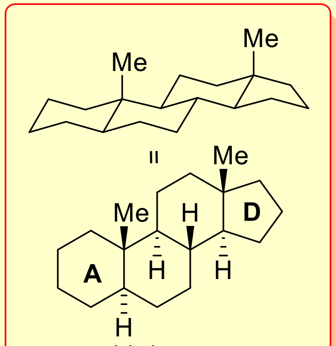
NB. most nucleophilic, primary alcohol is NOT protected

  - S. V. Ley *et al.* ‘*Dispiroketals: a new functional group for organic synthesis*’ *Contemp. Org. Synth.* **1995**, *2*, 365 [DOI]

Kinetic Control – *1,2-diaxial processes*

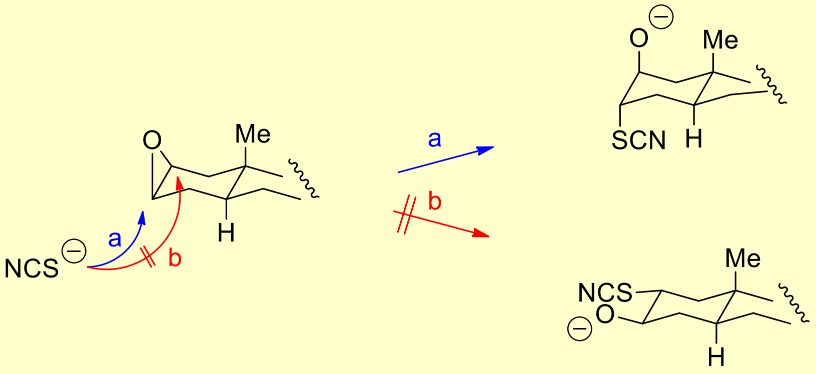
- *Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted* ***cyclohexanes:***
  - ***epoxide formation***: *e.g.* in A-ring of steroids (*NB.* No-ring flipping possible – rigid framework)

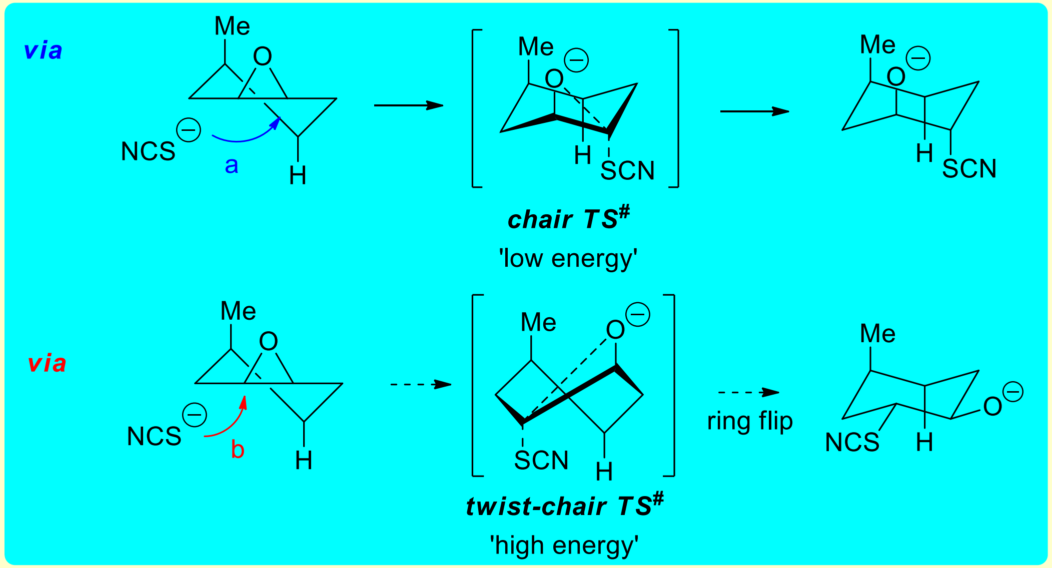




steroid ring system

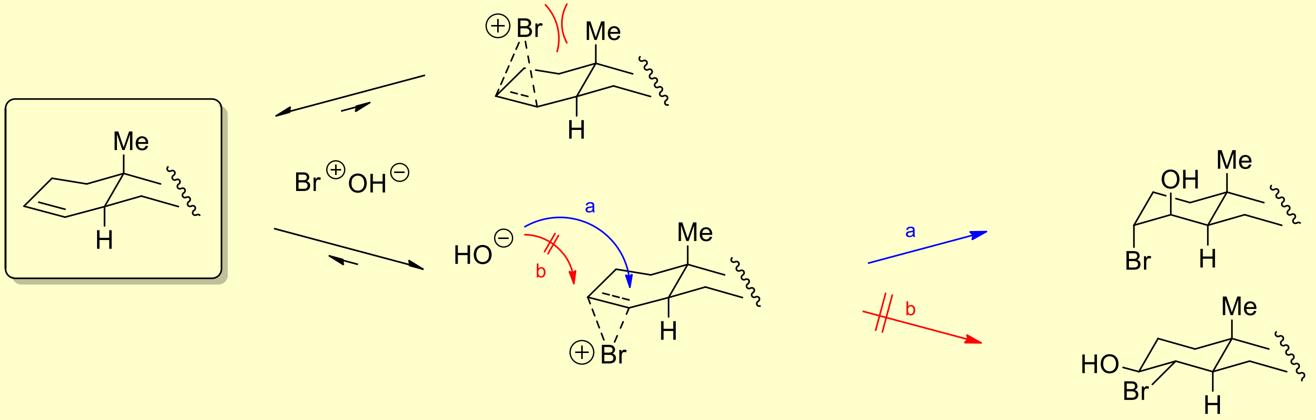
  - ***epoxide ring-opening***: *e.g.* in A-ring of steroids
    - Diaxial ring-opening (‘Fürst-Plattner’ rule) controls regioselectivity of nucleophilic attack





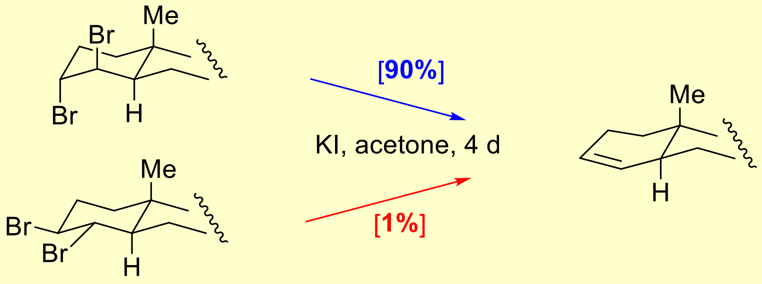
Kinetic control – *1,2-diaxial processes*

- *Attainment of anti-periplanar overlap of orbitals in 1,2-disubstituted* ***cyclohexanes:***
  - ***HOBr addition***: *e.g.* in A-ring of steroids



via twist-chair TS$^{\#}$

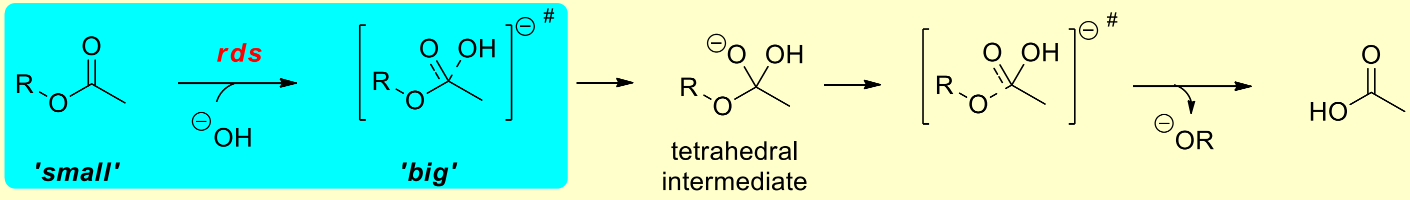
  - ***E2 elimination***: *e.g.* in A-ring of steroids



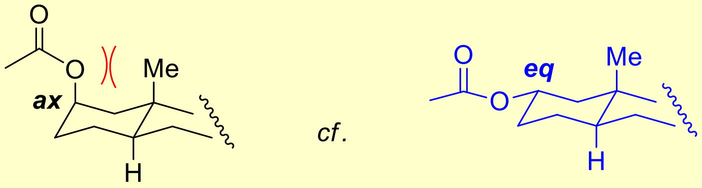
Steric/strain effects - *1,3-diaxial compression*

- Equivalent reactions of axial *vs*. equatorial substituents on cyclohexanes can differ substantially in rate when the ***rate-determining Transition State*** have different steric demands ('volume of activation') to the starting functional groups. There are two cases:

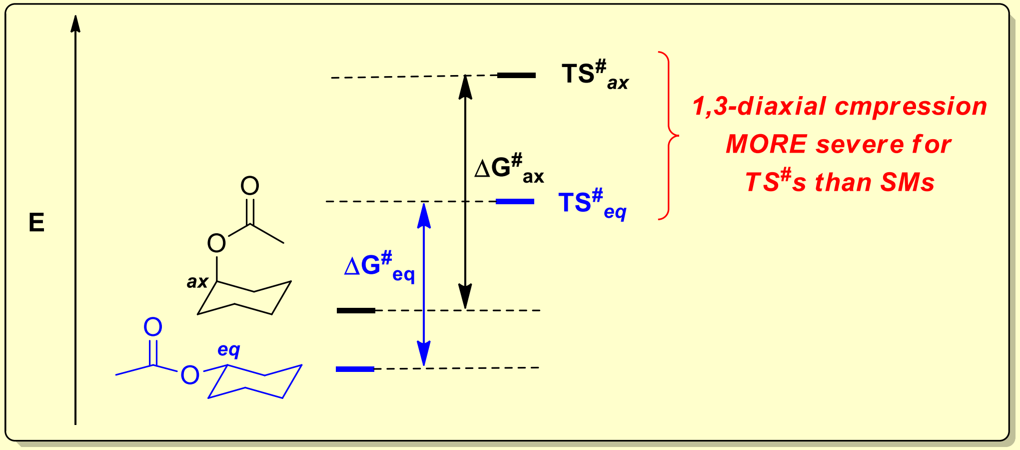
- ***The Transition State (TS$^\#$) is <u>MORE</u> crowded than the Starting Material (SM)***
  - *e.g.* base hydrolysis of esters:



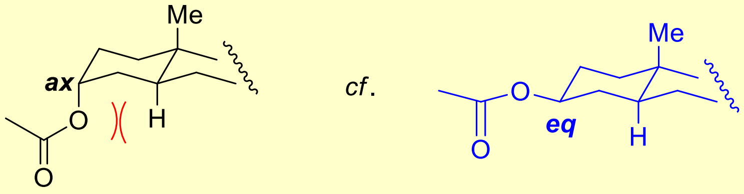
  - For axial and equatorial positions on cyclohexanes:



1 relative rate (NaOH, 80 °C) **10**



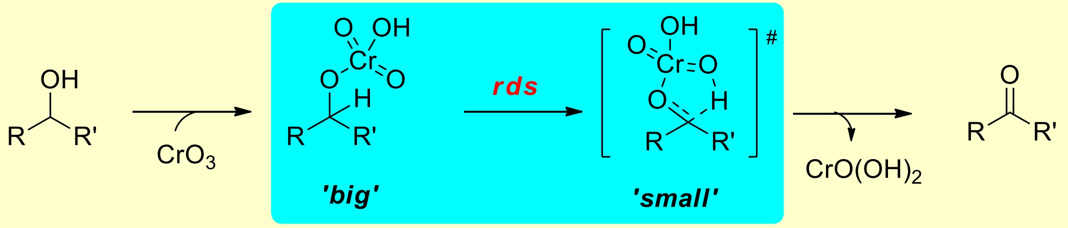
1,3-diaxial cmpression MORE severe for TS$^\#$s than SMs



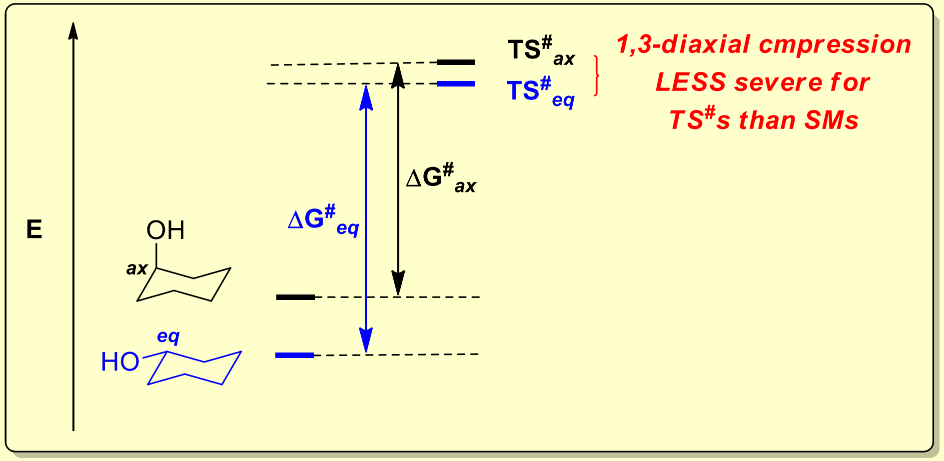
1 relative rate (NaOH, 80 °C) **3**

Steric/strain effects - *1,3-diaxial compression cont.*

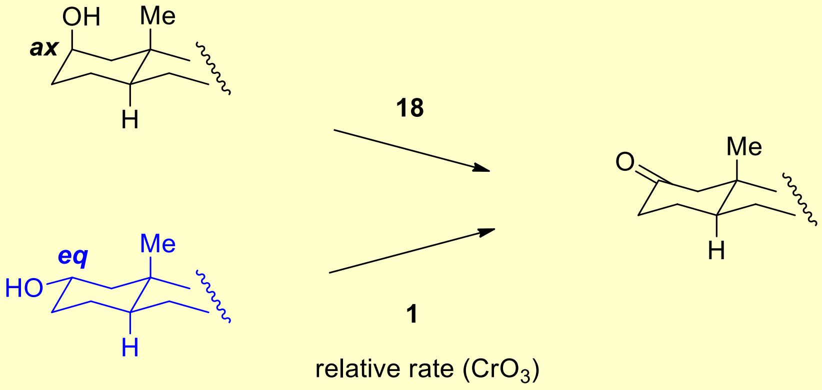
- ***The Transition State (TS$^{\#}$) is <u>LESS</u> crowded than the Starting Material (SM)***
  - *e.g.* Oxidation of alcohols:



  - For axial and equatorial positions on cyclohexanes:



1,3-diaxial cmpression LESS severe for TS$^{\#}$s than SMs



  - For a recent discussion of this 'strain-release CH activation' see: Eschenmoser & Baran *Angew. Chem. Int. Ed* **2009**, *48*, 9705 [DOI]

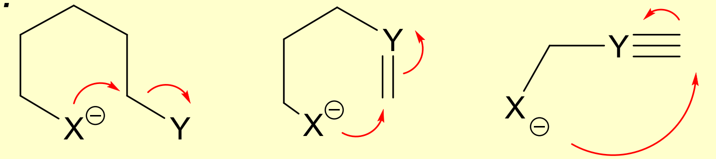
Baldwin's Rules for Ring Closure

- ***For <u>kinetically</u> controlled ring closures:***
  - Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734 [DOI] & *ibid* 736 [DOI] & *ibid* 738 [DOI]
  - For a review see: Gilmore *Chem. Rev.* **2011**, *111,* 6513 [DOI]
  - the relative facility of ring-closure depends critically on the ring size, the hybridisation of the reacting centres & the mode of ring-closure (*exo* or *endo*)

nomenclature

Exo - the bond being broken in the ring closure is exocyclic *i.e.* outside the ring
Endo - the bond being broken in the ring closure is endocyclic *i.e.* inside the ring
Tet - electrophilic centre has sp^3 hybridisation
Trig - electrophilic centre has sp^2 hybridisation
Dig - electrophilic centre has sp hybridisation

e.g.

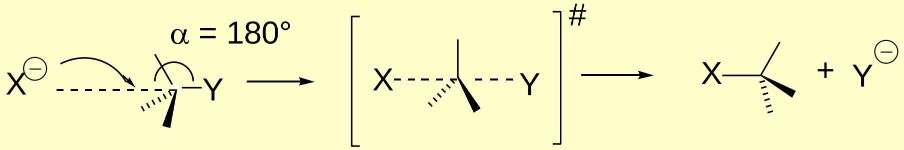


6 - exo - tet ***6 - endo - trig*** ***4 - endo - dig***

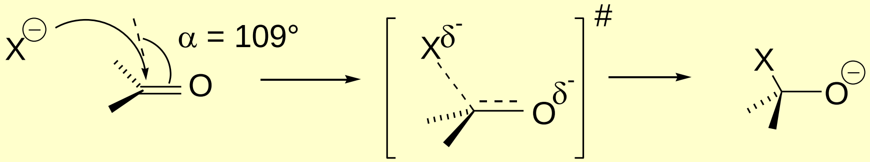
- <u>tetrahedral systems</u>:
  - 3 to 7-*exo-tet* are all favoured processes
  - 5 to 6-*endo-tet* are disfavoured
- <u>trigonal systems</u>:
  - 3 to 7-*exo-trig* are all favoured processes
  - 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured
- <u>digonal systems</u>:
  - 3 to 4-*exo-dig* are disfavoured processes; 5 to 7-*exo-dig* are favoured
  - 3 to 7-*endo-dig* are favoured

Baldwin's Rules for Ring Closure cont.

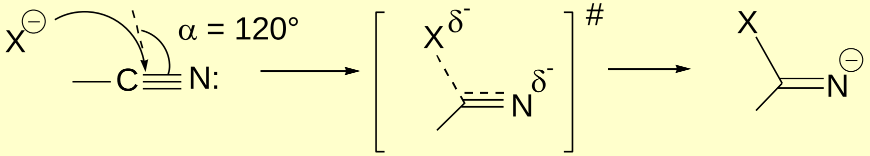
- ***Baldwin's rules were formulated following analysis of transition state geometries:***
  - Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734 [**DOI**] & *ibid* 736 [**DOI**] & *ibid* 738 [**DOI**]
  - ***Tet*** *- electrophilic centre has* sp^3 *hybridisation - S_N2 reaction*
    - evidence for this trajectory see: Eschenmoser *Helv. Chim. Acta* **1970**, *53*, 2059 [**DOI**]



  - ***Trig*** *- electrophilic centre has* sp^2 *hybridisation - Nucleophilic addition to carbonyl/imine*
    - evidence for this trajectory see: Burgi *J. Am. Chem. Soc.* **1973**, *95*, 5065 [**DOI**] & Proctor & Dunnitz *Helv. Chim. Acta* **1981**, *64,* 471 [**DOI**]



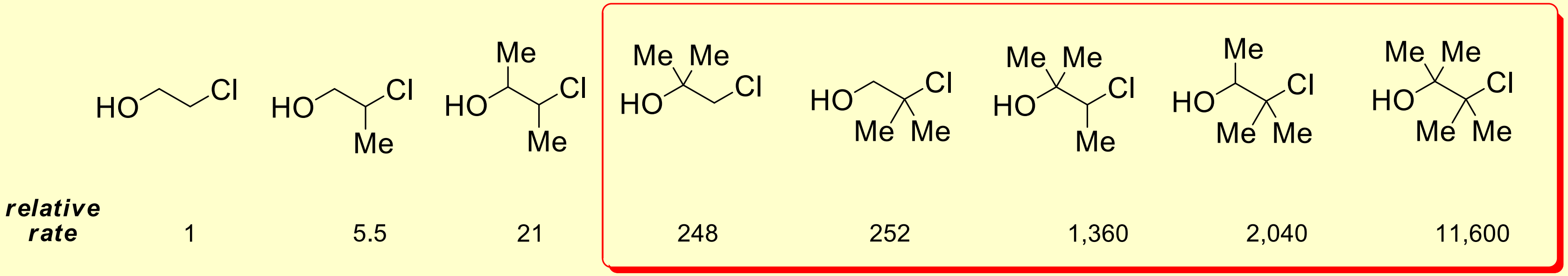
  - ***Dig*** *- electrophilic centre has sp hybridisation - Nucleophilic addition to nitrile/alkyne*
    - evidence for this trajectory see: Procter *Helv. Chim. Acta* **1978**, *61*, 2538 [**DOI**] & **1981**, *64*, 471 [**DOI**]



The Thorpe-Ingold Effect

- ***The gem-dialkyl (Thorpe-Ingold effect) refers to the relative ease with which ring-closure can be achieved for small & medium rings when such a group is present in the tethering chain***
  - Thorpe & Ingold *J. Chem. Soc., Trans.* **1915**, 1080 [**DOI**]
  - The effect is generally considered to be a ***kinetic*** phenomenon which has been attributed to:
    1. The *gem*-substituents compressing the angle between the two substituents bearing the reactive end groups thereby bringing them closer together
    2. The *gem*-substituents increasing the solution population of *gauche* conformers in which the reactive ends are close together
    3. The *gem*-substituents hindering solvation of the reactive centre (*e.g*. In epoxide formation, see below)
  - ***Thermodynamic*** factors (*e.g.* entropy) have also been invoked but most evidence suggests that this is usually a negligible component (see: Bachrach *J. Org. Chem*. **2008**, *73*, 2466 [**DOI**])

  - *e.g.* For hydroxide-catalysed epoxide formation (see: Jorgensen *J. Am. Chem. Soc.* **2010**, *132*, 8766 [DOI])



  - Synthetically, the following (non-alkyl) groups are also useful for promoting cyclisation in the same manner: