Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURES 2 & 3
Ring synthesis: cyclocondensations and cycloadditions

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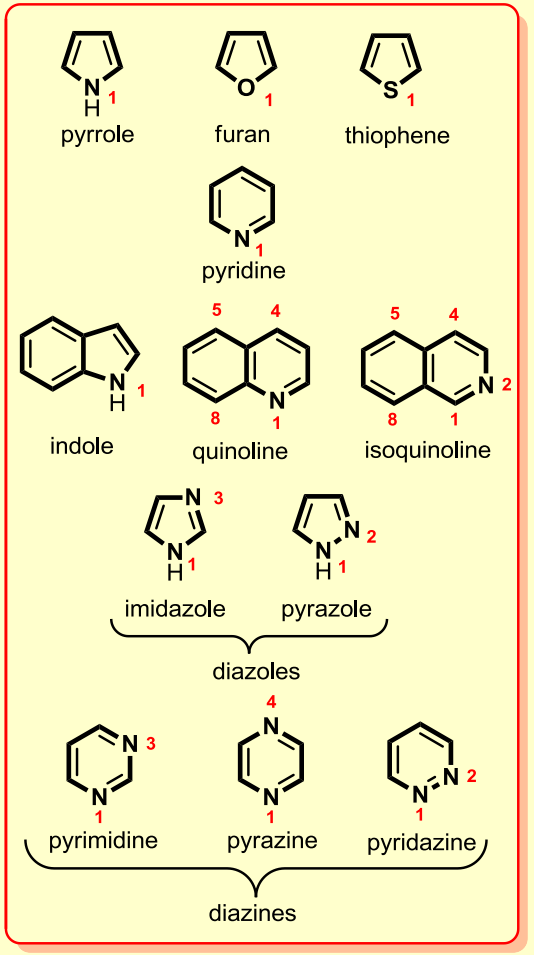
Format & scope of lectures 2 & 3

- ***Ring synthesis:***
  - cyclisations *vs.* cycloadditions

- ***Cyclisation/cyclocondensation reactions***
  - essential functional group chemistry
    - imines & enamines
    - carbonyls, enols & enol ethers
    - thiocarbonyls, ene thiols & thioenol ethers
  - kinetics & thermodynamics of ring closure
  - common strategies for cyclisations
    - 5-membered rings
    - 6-membered rings
  - design considerations

- ***Cycloaddition reactions***
  - 5-membered rings – 1,3-dipolar cycloadditions [3+2]
  - 6-membered rings – *hetero*-Diels-Alder reactions [4+2]

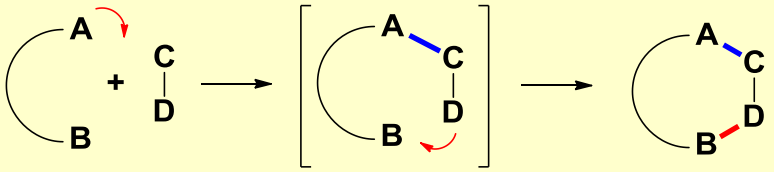
- ***Supplementary slides 1-7***
  - some background information



Two Distinct Strategies for Ring Formation

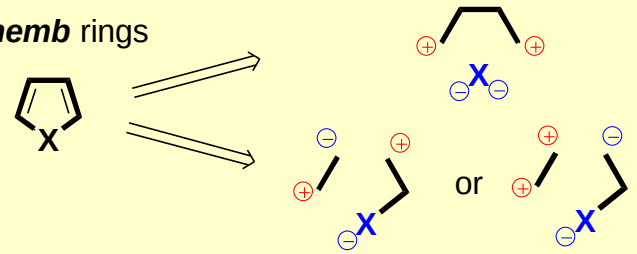
- There are **2** distinct ways in which heterocyclic aromatic compounds can be prepared:

Cyclisation reactions of acyclic substrates

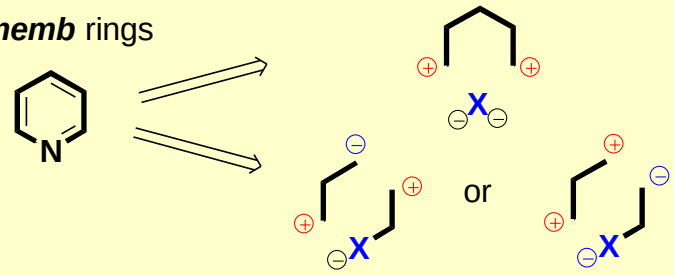


- ***stepwise*** formation of linear ***cyclisation precursor***
- formation of ***1 new bond*** during ring-closure
- C-C or C-het bond
- triggered by nucleophiles, electrophiles, radicals *etc.*

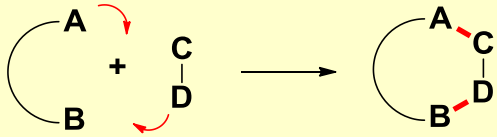
5-memb rings



6-memb rings

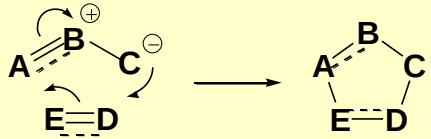


Cycloaddition reactions

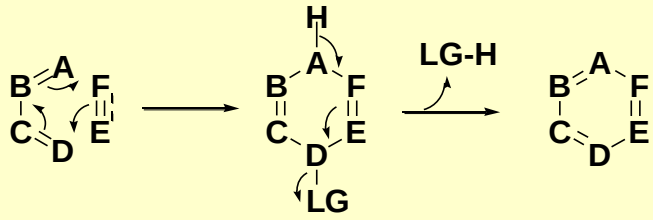


- ***concerted*** formation of ***2 new bonds***
- Pericyclic mechanism
- C-C and/or C-het bonds
- convergent (efficiency, diversity)

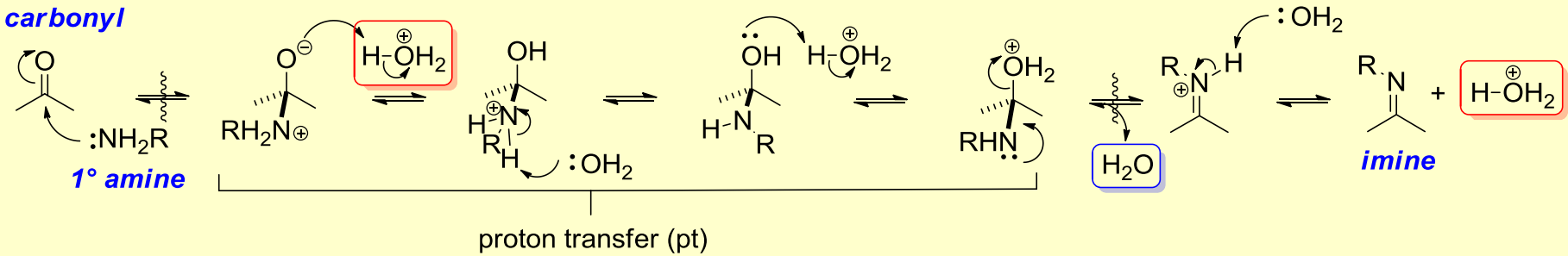
1,3-dipolar cycloadditions give ***5-memb*** rings



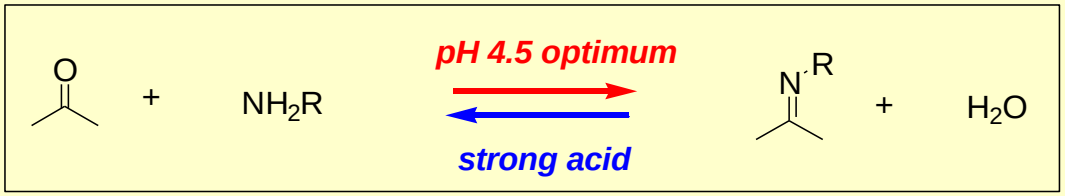
hetero-Diels-Alder reactions give ***6-memb*** rings



- ***Imines –*** *formation:*
  - ***carbonyl + 1° amine → imine:***



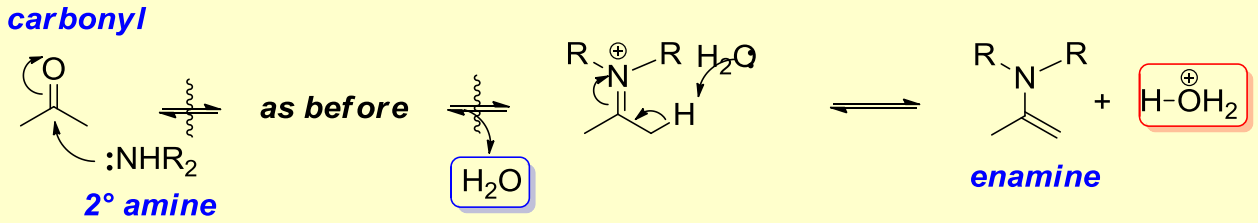
  - ***overall:***



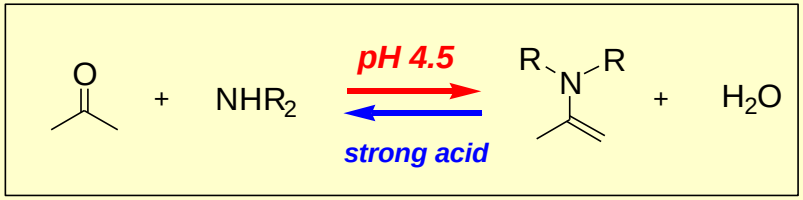
    - need H^+ but if too much acid is present → protonates amine → stops nucleophilic addition. pH 4.5 is a compromise. For the reverse process, low pH → fast,~irreversible reaction (amine protonated → salt)

  - ***reversible:***
    - carbonyl form is thermodynamically most stable (C=O ~749 $kJmol^{-1}$ *cf.* C=N ~607 $kJmol^{-1}$)
    - need to drive off water (*i.e.* a *dehydration*/*condensation* reaction):
      - heat (>100 °C for H_2O)
      - 3 Å MS (Molecular Sieves) – zeolites
      - azeotropic distillation – 'Dean-Stark trap' (*e.g.* benzene – H_2O)
      - chemical dehydration – *e.g.* $POCl_3$ or *c.*H_2SO_4

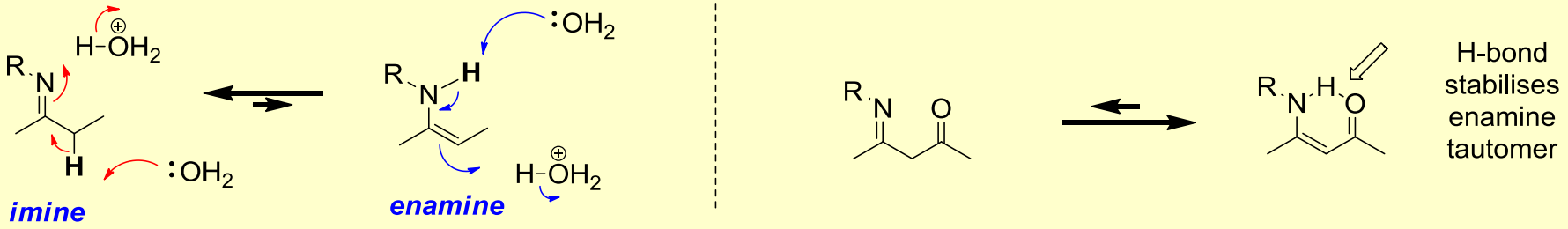
- ***Enamines –*** *formation:*
  - ***carbonyl + 2° amine → enamine:***
    - last step is different:



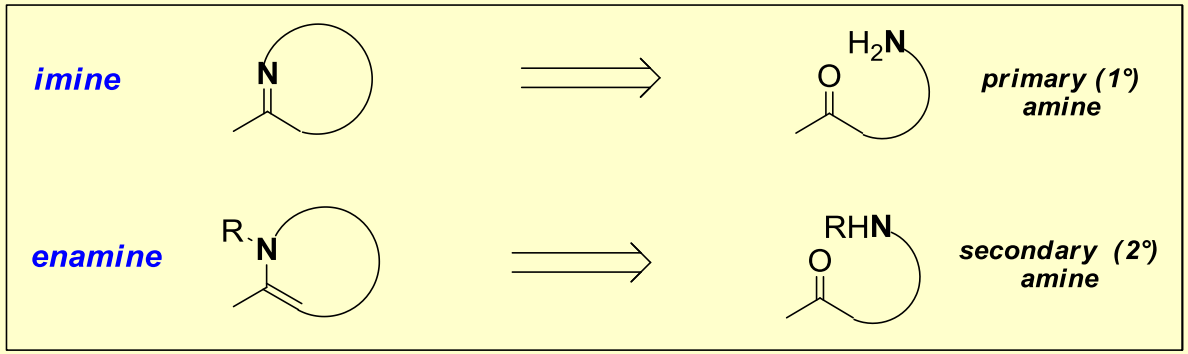
  - ***overall:***



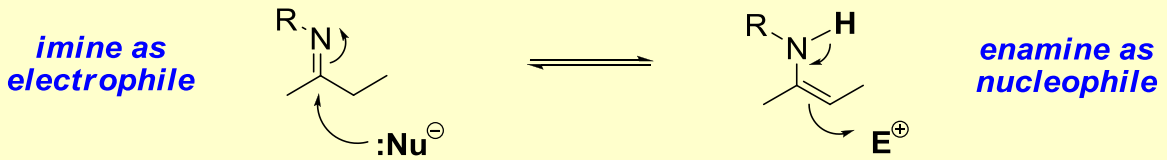
  - ***of course, imines can also form an enamine tautomer***
    - but usually the imine form is preferred thermodynamically…except in special circumstances



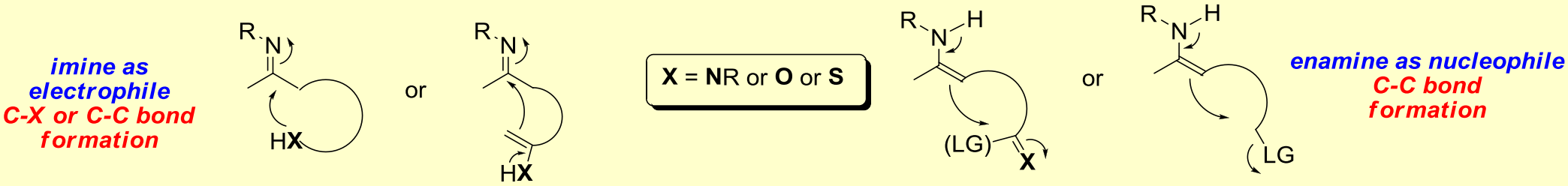
- ***Imines & enamines*** – *intramolecular formation, i.e. ring-closure:*
  - retrosynthetic analysis:



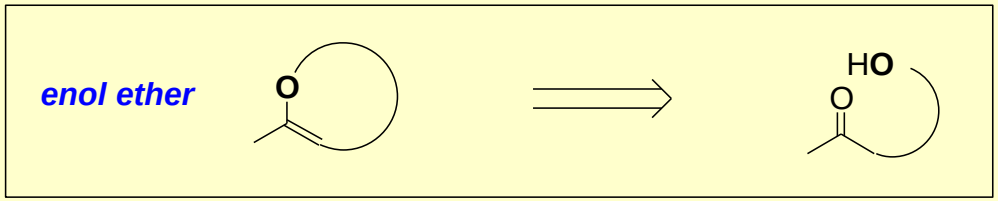
- ***Imines & enamines -*** *reactivity:*
  - ***imines are ELECTROPHILES; enamines are NUCLEOPHILES:***



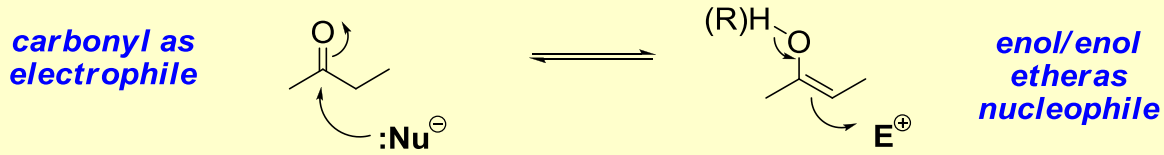
  - ***Intramolecular reactions can lead to ring-closure...***



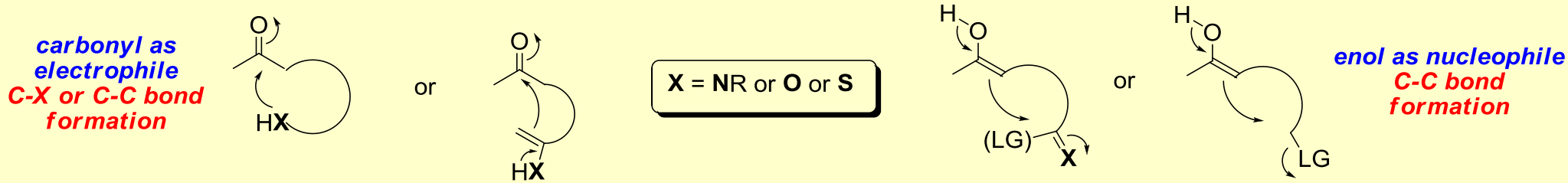
- ***Carbonyls, enols & <u>enol ethers</u>*** *– intramolecular formation, i.e. ring-closure:*
  - retrosynthetic analysis:



- ***Carbonyls, enols & enol ethers –*** *reactivity:*
  - ***carbonyls are ELECTROPHILES; enols & enol ethers are NUCLEOPHILES:***



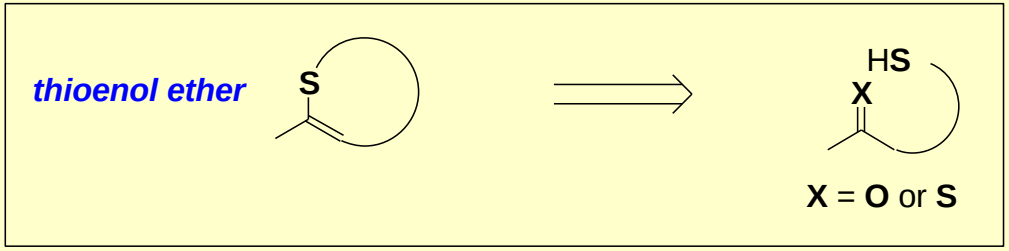
  - ***Intramolecular reactions can lead to ring-closure...***



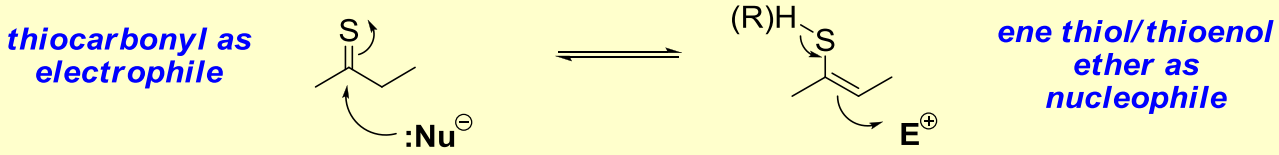
  - ...revise acid and base catalysed ***aldol reactions*** (see supplementary slides 1-2)

Cyclisation Reactions *- Essential Functional Group Chemistry – thiocarbonyls & ene thiols*

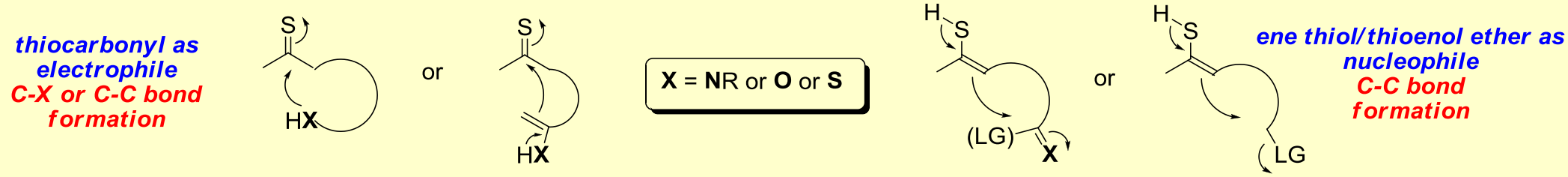
- ***Thiocarbonyls, ene thiols & thioenol ethers*** *– intramolecular formation, i.e. ring-closure:*
  - retrosynthetic analysis:



- ***Thiocarbonyls, ene thiols & thioenol ethers –*** reactivity:
  - ***thiocarbonyls are ELECTROPHILES; ene thiols & thioenol ethers are NUCLEOPHILES:***

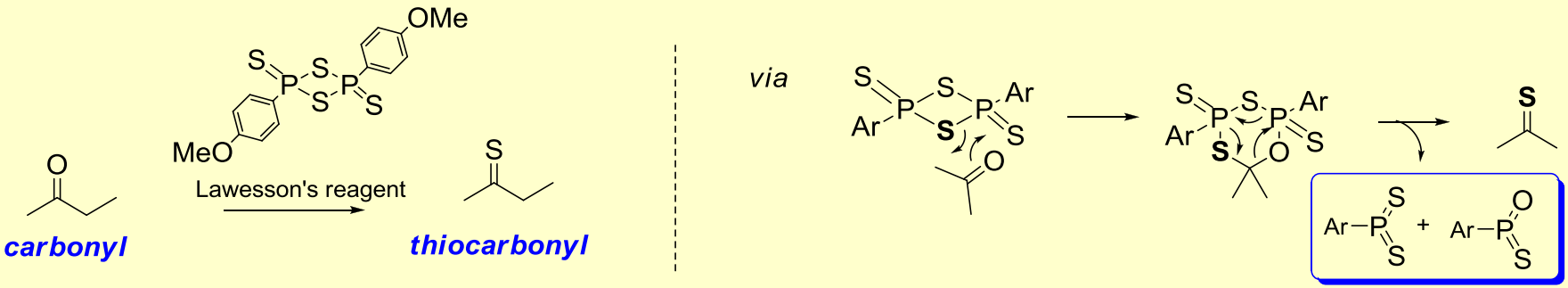


  - ***Intramolecular reactions can lead to ring-closure...***

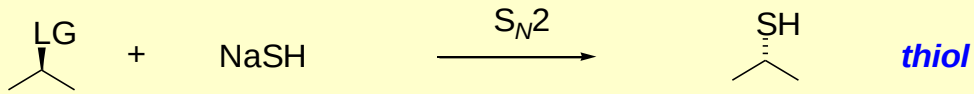


    - *thiols* are MORE nucleophilic than *alcohols* & *thiocarbonyls* are MORE electrophilic than *carbonyls*

- ***Thiocarbonyls, ene thiols & thioenol ethers –*** *formation:*
  - ***thiocarbonyls are generally prepared from the corresponding carbonyl compounds:***
    - typically use P_2S_5 or Lawesson's reagent (**e-EROS**):



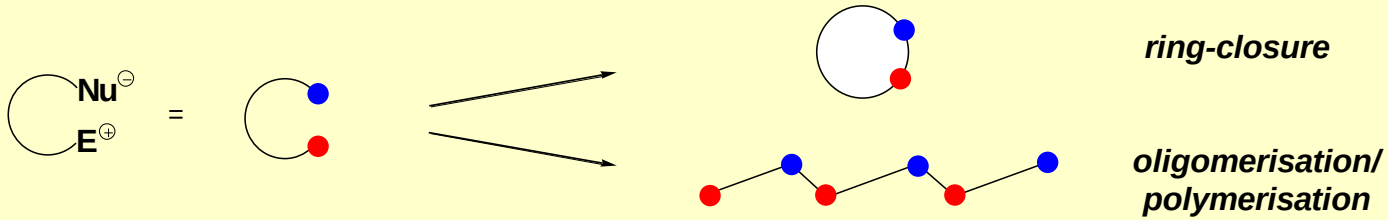
    - reactions driven by strength of P=O *vs.* P=S bond
  - ***thiols are generally formed by substitution of a leaving group (LG):***



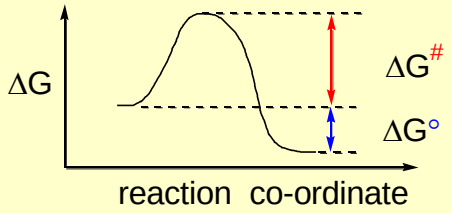
  - ***CAUTION... most thiol and thiocarbonyl compounds STENCH!***

Cyclisation Reactions – *Thermodynamics & Kinetics of Ring Closure*

- *Intra*-molecular ***ring-closure*** *vs. inter*-molecular ***oligomerisation/polymerisation:***



  - ***entropy is the key factor:***
    - ***concentration of the reaction*** – high dilution favours ring-closure
    - ***ring size formed*** – smaller rings favoured (but...see below)



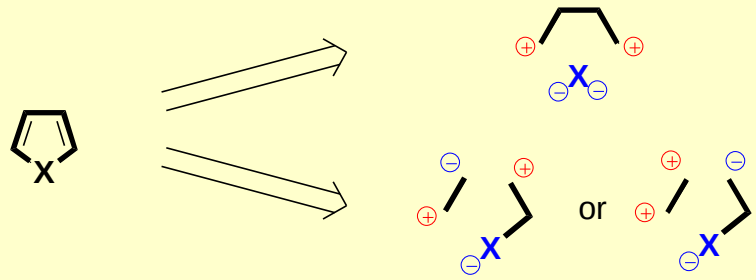
$\Delta G^{\#}$ ***free energy of activation:*** $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$

ΔG° ***free energy of the reaction:*** $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$

- ***Ring-closure*** under ***thermodynamic (TD) control*** (*i.e.* reversible conditions):
  - many reactions forming heteroaromatic products are driven by:
    - favourable ΔS° due to loss of small molecule (as vapor at high temperature → irreversible)
    - *i.e.* cyclo*dehydrations* ($-H_2O$) & cyclo*condensations* ($-H_2S$, NH_3, MeOH *etc.*)
    - favourable ΔH° due to stability of aromatic product
- ***Ring-closure*** under ***kinetic control*** (*i.e.* irreversible conditions):
  - less common when forming heteroaromatic products, but does affect the rate of TD controlled reactions:
    - variable $\Delta S^{\#}$ - critically dependent on ring size & hybridisation of reacting centres - ***Baldwin's rules*** (see supplementary slides 3-4)

Cyclisation Reactions – *Common Strategies for 5-Membered Rings*

- ***2 common strategies for cyclisations:***

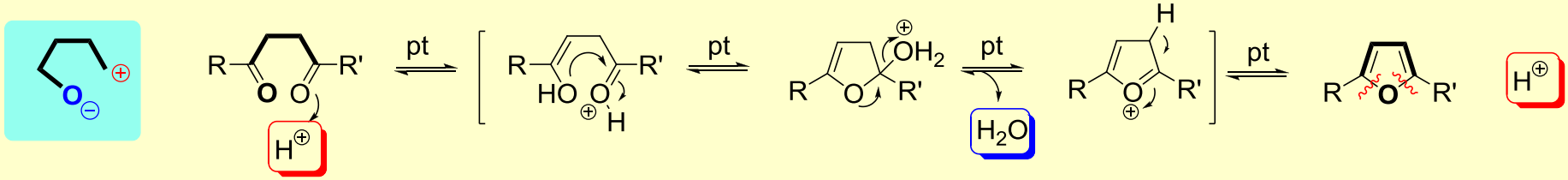


TYPE I: ***2 x C-X bond formation***

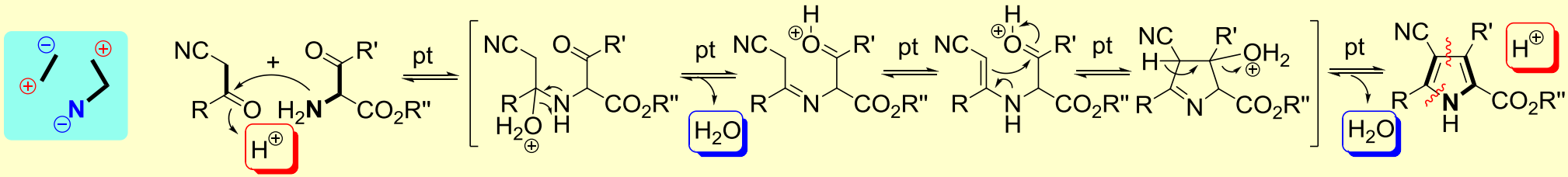
TYPE II: ***1 x C-X bond & 1 x C-C bond formation***

  - for synthetic equivalents of these ‘synthons’ and others (see supplementary slide 5)

TYPE I: ***e.g. Paal-Knorr furan synthesis***



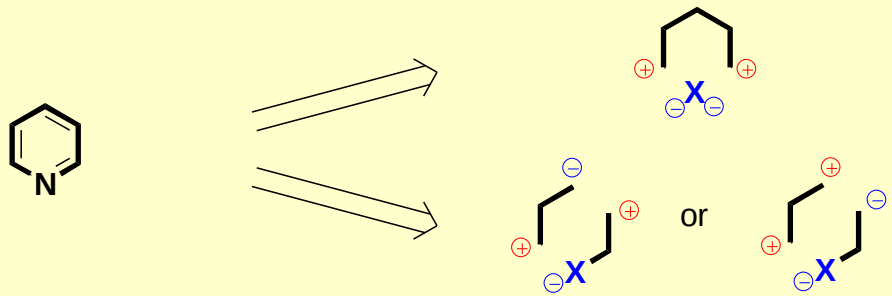
TYPE II: ***e.g. Knorr pyrrole synthesis***



  - the exact sequence of individual steps for most cyclocondensation reactions is unknown and will vary with reaction conditions (solvent, temperature, pH *etc.*) – seek *plausible* pathways

Cyclisation Reactions – *Common Strategies for 6-Membered Rings*

- ***2 common strategies for cyclisations:***

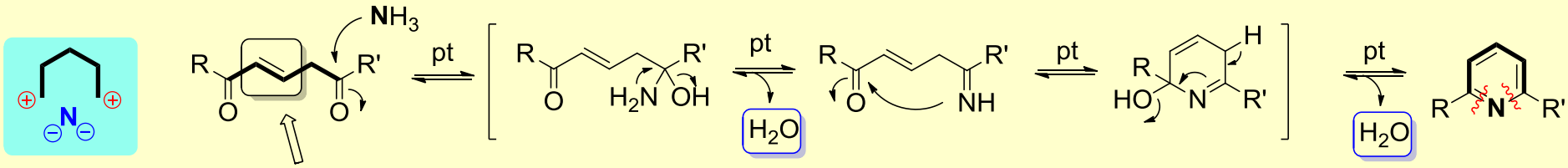


TYPE I: ***2 x C-X bond formation***

TYPE II: ***1 x C-X bond & 1 x C-C bond formation***

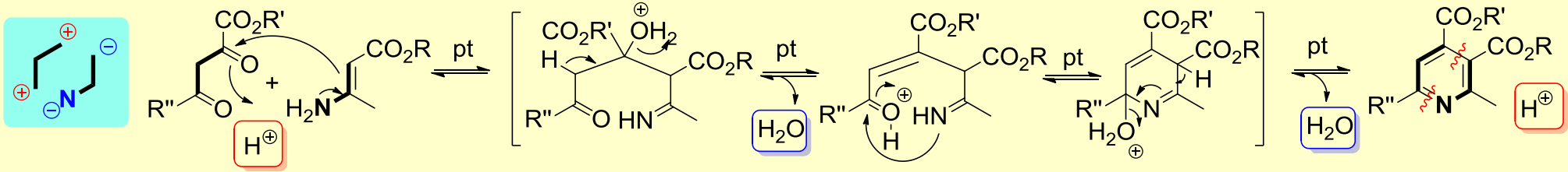
- for synthetic equivalents of these ‘synthons’ and others (see supplementary slide 5)

TYPE I: ***e.g. 'Paal-Knorr' pyridine synthesis***



NB. unsaturation in 1,5-dicarbonyl obviates the need for oxidation (see next slide)

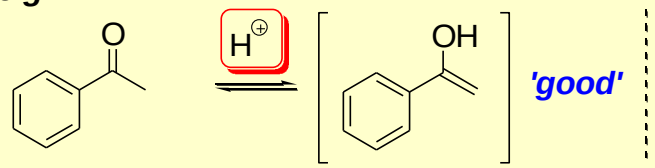
TYPE II: ***e.g. enamine/1,3-dicarbonyl pyridine synthesis***



Cyclisation Reactions – *Design Considerations*

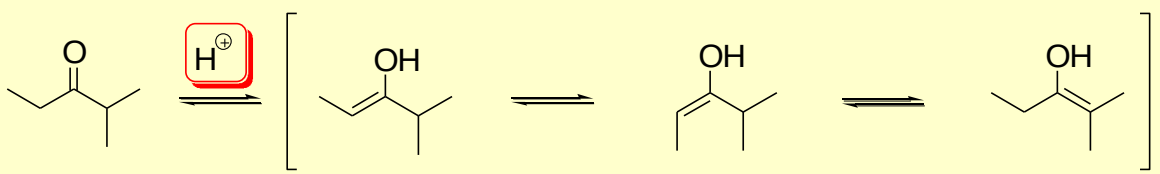
- ***Considerations during retrosynthetic analysis – synthesis design:***
  - identify ***strategic bond disconnections*** – seek maximum convergence
    - identify ***synthons*** with simple, readily available ***synthetic equivalents*** (see supplementary slide 5)
    - avoid substrates with multiple possible enol/enolate forms:

e.g.



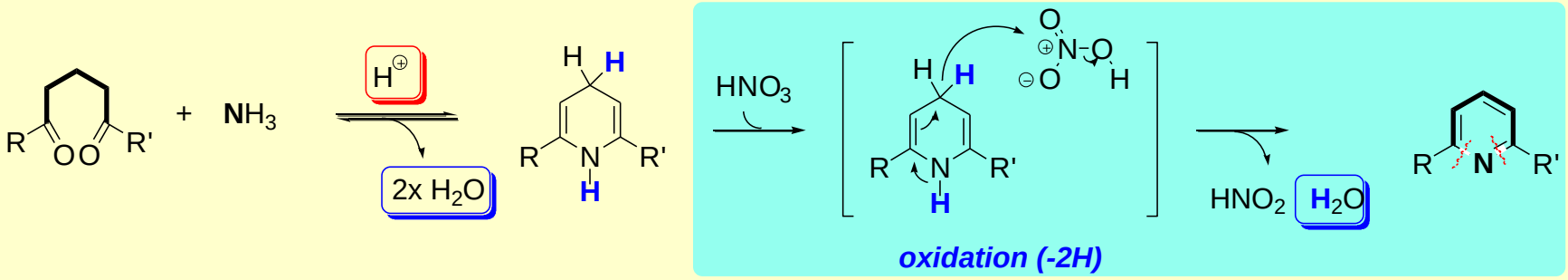
'good'

cf.



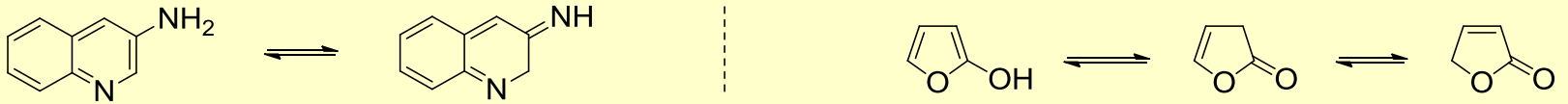
'bad'

  - pay attention to oxidation level – is the degree of unsaturation correct to avoid need for oxidation?



  - what functional groups are required?...introduce before, or after ring formation?

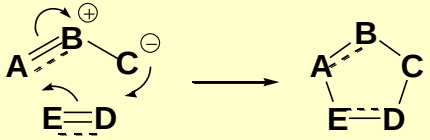
- Look out for different ***tautometic forms*** of intermediates & products (see supplementary slides 6-7)



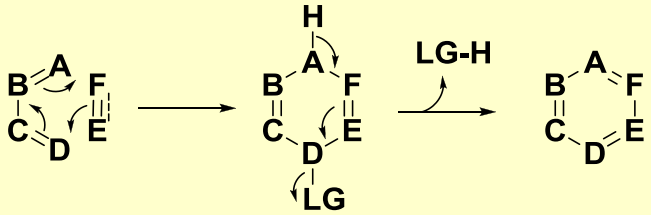
Cycloaddition Reactions *– General Features*

- ***Cycloaddition reactions are characterised by:***
  - ***concerted*** formation of ***2 new bonds*** (C-C and/or C-het) – no reaction intermediates
  - asynchronous bond formation – *i.e.* some build up of charge in transition state as the formation of some bonds is more advanced than that of others
  - 'aromatic' transition state [(4n + 2) π electrons involved] – pericyclic reactions
  - convergent (efficiency, diversity) but need to control ***regiochemistry*** (see later)

- ***5-Membered rings*** are formed from ***1,3-dipolar cycloadditions*** {[$\pi_{4s}+\pi_{2s}$] pericyclic processes}
  - reaction of ***1,3-dipole*** with ***dipolarophile***
  - initial products can be ***aromatic*** or require subsequent elimination/oxidation → ***aromatisation***

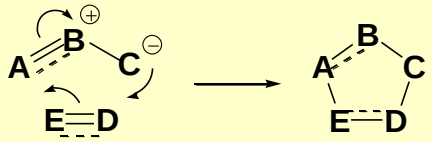


- ***6-Membered rings*** are formed from ***hetero-Diels-Alder reactions*** {[$\pi_{4s}+\pi_{2s}$] pericyclic processes}
  - reaction of ***diene*** with ***dienophile***
  - initial products are ***di- or tetrahydro intermediates –*** subsequent elimination/oxidation → ***aromatisation***



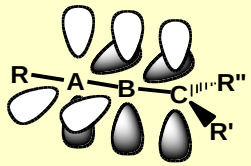
Cycloaddition Reactions – *1,3-Dipolar Cycloadditions → 5-Membered Rings*

- ***1,3-Dipolar cycloadditions are 6 electron [π_{4s} + π_{2s}] concerted pericyclic reactions:***
  - sometimes referred to as [3+2]-cycloadditions – this refers to the number of ATOMS (<u>not</u> electrons)



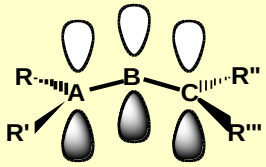
- ***There are 2 main classes of dipoles used in 1,3-dipolar cycloadditions:***

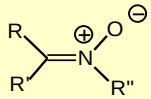
LINEAR 1,3-DIPOLES



NITRILE OXIDES	R—C≡N—O	***ISOXAZOLES***
NITRILE IMINES	R—C≡N—NR	***PYRAZOLES***
NITRILE SULFIDES	R—C≡N—S	***ISOTHIAZOLES***
DIAZO COMPOUNDS	N≡N—CR_2	***PYRAZOLES***
AZIDES	N≡N—NR	***TRIAZOLES***

TRIGONAL 1,3-DIPOLES





NITRONES

ISOXAZOLES

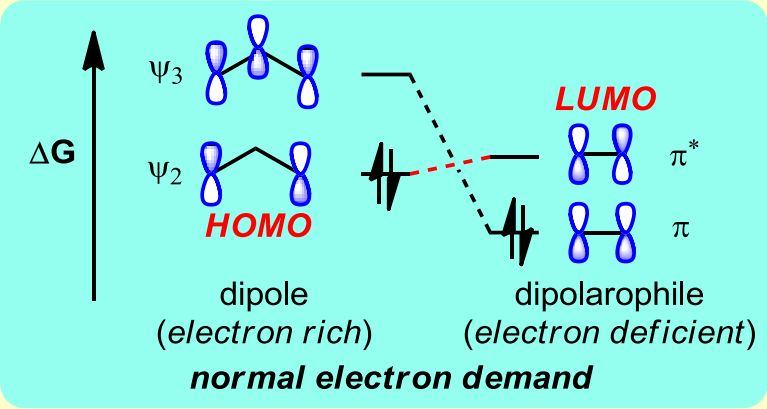
<u>notes</u>

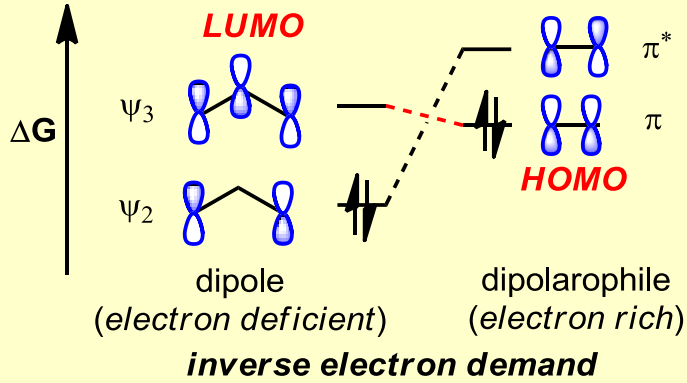
- 3 atom/4π electron species
- central atom ≠ C
- always have formal charges
- charges @ 1,2- NOT 1,3-positions
- <u>linear</u> are: sp-sp-sp^2
- <u>trigonal</u> are sp^2-sp^2-sp^2
- no correlation between reactivity & geometry
- retrosynthetic 'signature' is ≥2 adjacent heteroatoms in the ring

- ***Most multiple bonds can act as dipolarophiles:***
  - BUT usuallya C=C bond...

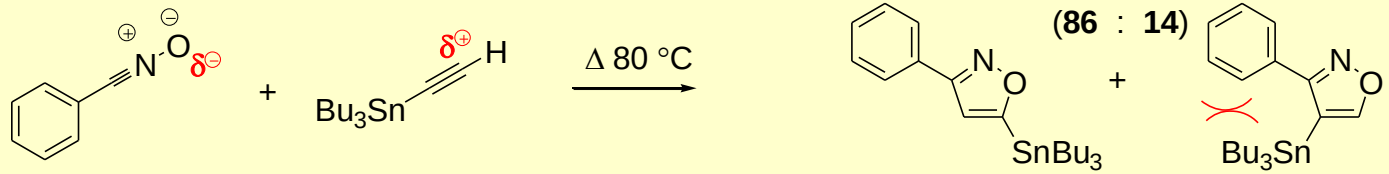
C=C C≡C C=O C=N C≡N

- ***Reactivity*** is controlled by relative energies of Frontier Molecular Orbitals (FMOs)
  - the key interaction is between the Highest Occupied Molecular Orbital (HOMO) of one reactant and the Lowest Unoccupied (*i.e.* empty) Molecular Orbital (LUMO) of the other reactant
    - the closer the two interacting orbitals are in energy the faster the reaction rate
    - consequently, 2 important types can be identified:





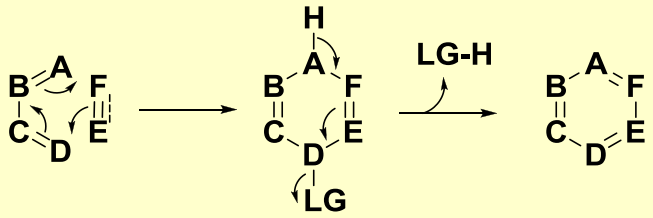
- ***Regiochemistry*** is controlled by:
  - the polarity of the frontier molecular orbitals (as for hetero-Diels-Alder regioselectivity, see later)
  - BUT, sterics can override *e.g.*:



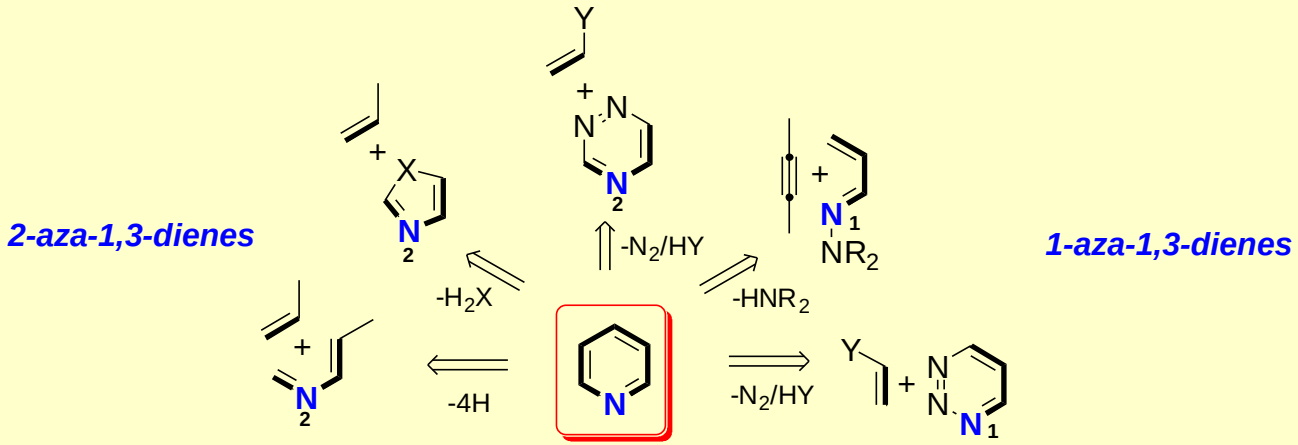
nitrile oxide (1,3-dipole) + ***alkyne*** (dipolarophile)

3,5- & 3,4-di-substituted isoxazoles

- ***hetero-Diels-Alder cycloadditions are 6 electron [π_{4s} + π_{2s}] concerted pericyclic reactions:***
  - sometimes referred to as [4+2]-cycloadditions – this refers to the number of ATOMS (<u>not</u> electrons)



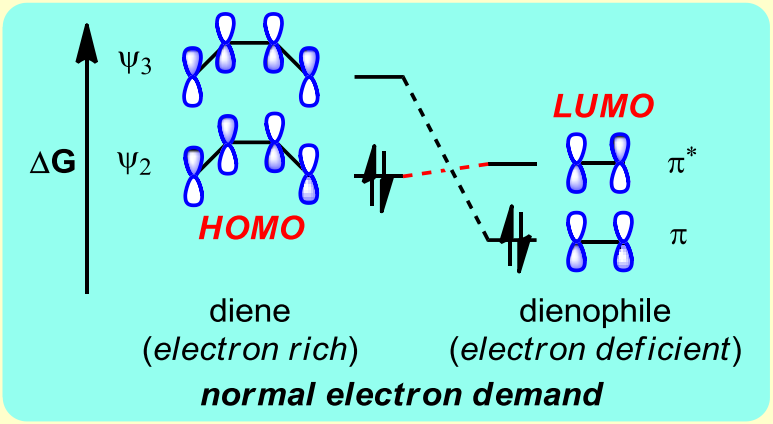
- ***Azines are generally prepared by aza-Diels-Alder*** reactions between <u>aza-1,3-dienes</u> and <u>alkenes/alkynes</u>
  - usually ***inverse electron demand***
  - generally give non-aromatic heterocycle → extrusion of small molecule(s) → aromatic species

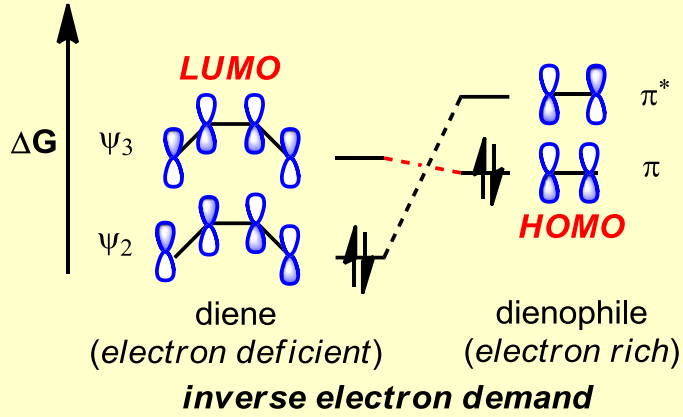


- ***Most multiple bonds can act as dienophiles:***

C=C C≡C C=O C=N C≡N

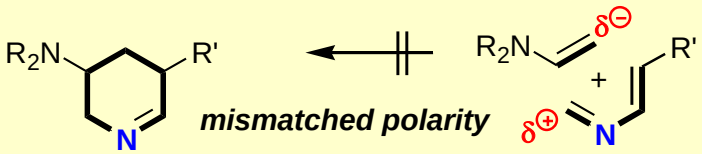
- ***Reactivity*** is controlled by the relative energies of the Frontier Molecular Orbitals (FMOs)
  - again, 2 important types:

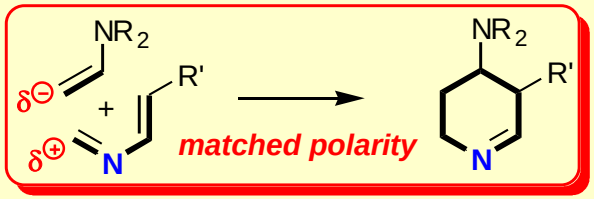




  - ***hetero-diene + all carbon dienophile*** ✓ usually ***inverse electron demand***
  - all carbon diene + hetero-dienophile ✓ usually ***normal electron demand***
  - hetero-diene + hetero-dienophile × *rare (tend to have alternative reaction paths available)*

- ***Regiochemistry*** is controlled by the polarity of the frontier molecular orbitals
  - electron donating and withdrawing substituents perturb energies and sizes of orbitals – most favourable reactions involve overlap of orbitals of similar size with complementary polarities:

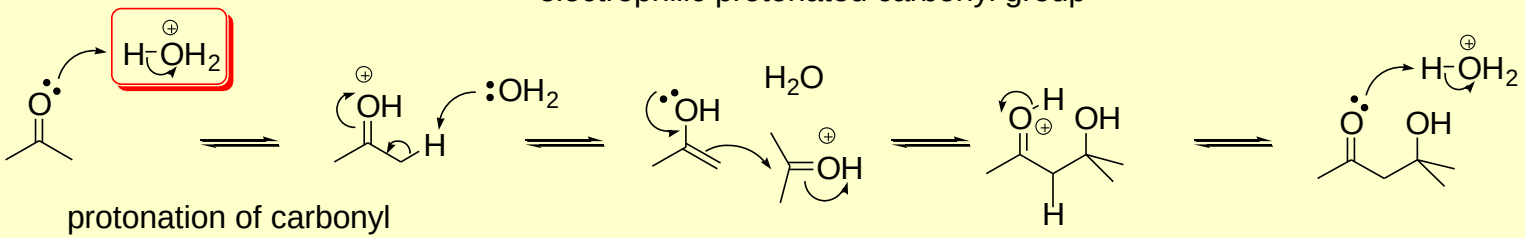




Supplementary slide 1 *- Essential Functional Group Chemistry – acid catalysed aldol reaction*

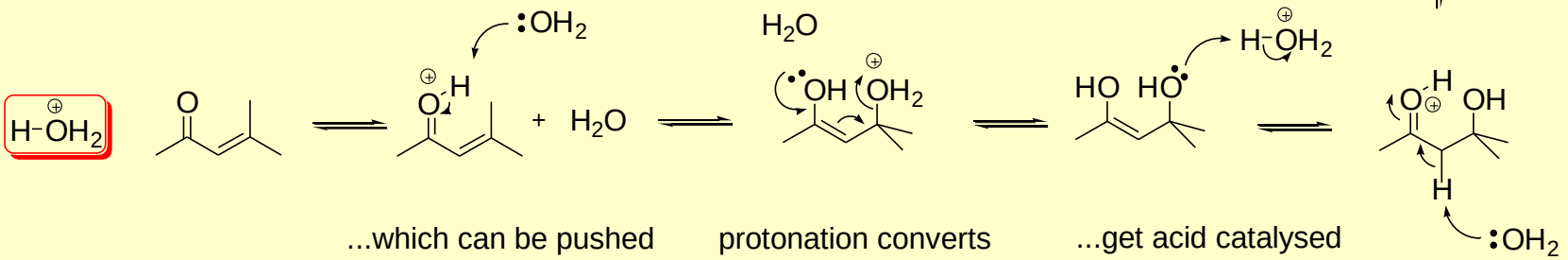
- ***The <u>acid</u> catalysed <u>aldol</u> reaction:***

nucleophilic enol reacts with highly electrophilic protonated carbonyl group



protonation of carbonyl leads to formation of enol

aldol; can stop here but under more forcing conditions.....

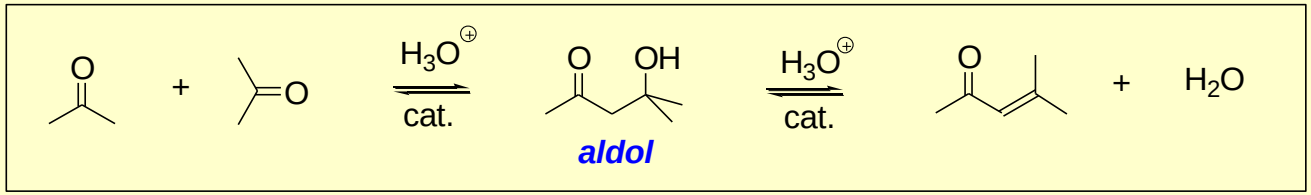


...which can be pushed out by the enol

protonation converts OH into a good LG....

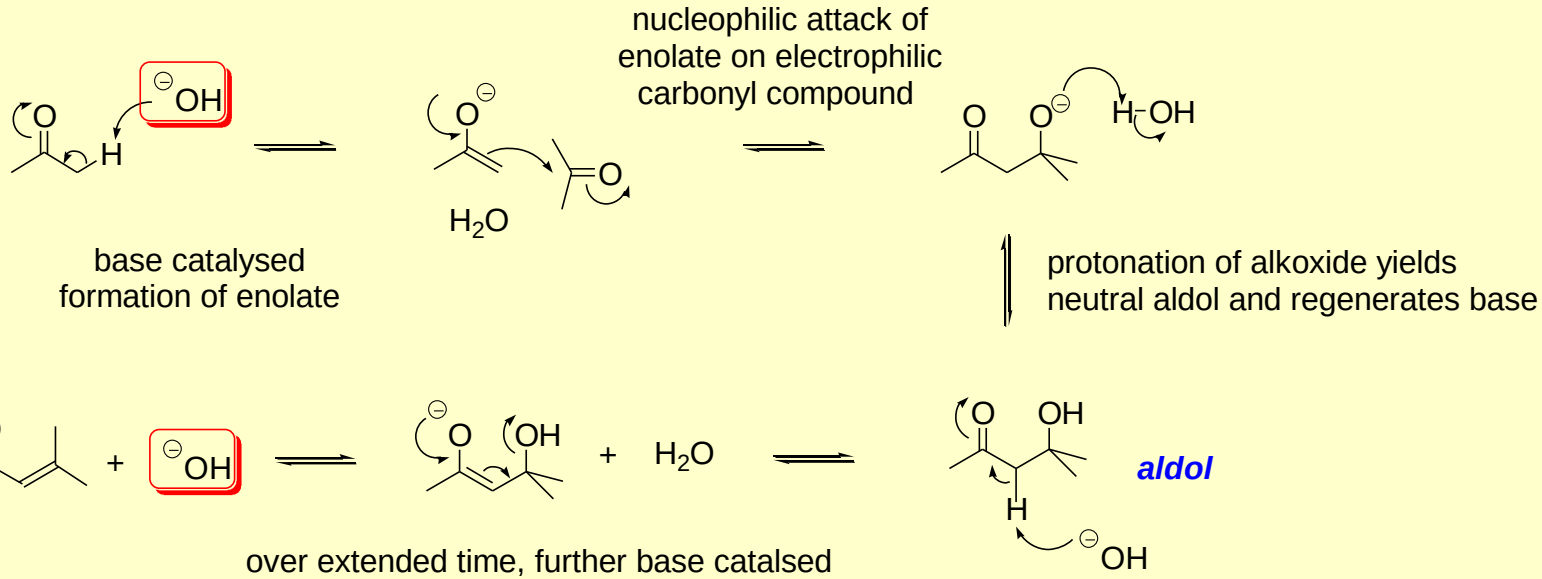
...get acid catalysed enolisation

- ***Overall:***

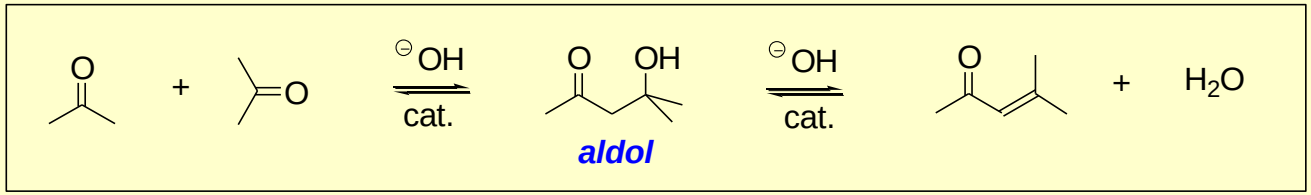


Supplementary slide 2 *- Essential Functional Group Chemistry – base catalysed aldol reaction*

- ***The <u>base</u> catalysed <u>aldol</u> reaction:***



- ***Overall:***



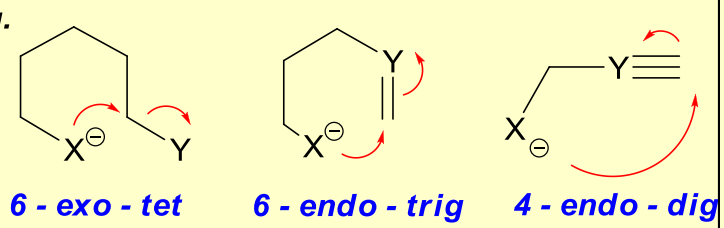
Supplementary slide 3 *– Baldwin's 'Rules for Ring Closure'*

- ***For <u>kinetically</u> controlled ring closures:***
  - Baldwin *J. Chem. Soc., Chem. Commun.* **1976**, 734 (DOI) & *ibid* 736 (DOI) & *ibid* 738 (DOI)
  - 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.



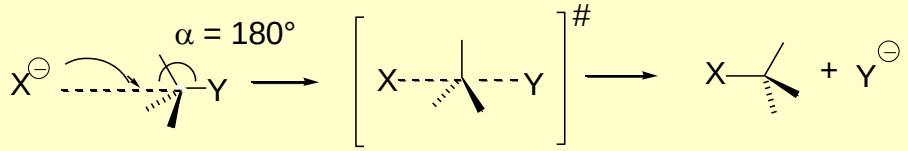
6 - exo - tet ***6 - endo - trig*** ***4 - endo - dig***

  - <u>tetrahedral systems</u>:
    - 2 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

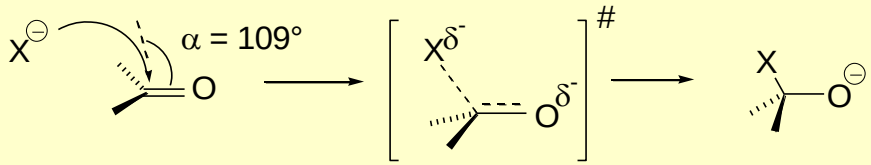
Supplementary slide 4 *– Baldwin's 'Rules for Ring Closure' cont.*

- 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]

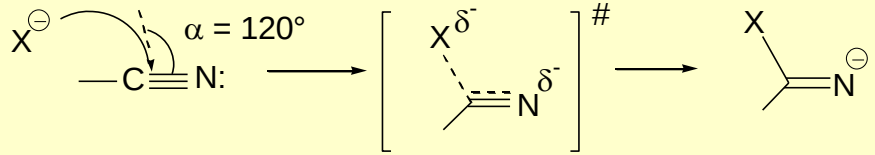
  - ***Tet*** *- electrophilic centre has sp³ hybridisation -* *S_N2 reaction*
    - evidence for this trajectory see: Eschenmoser *Helv. Chim. Acta* **1970**, *53*, 2059 [DOI]



  - ***Trig*** *- electrophilic centre has sp² 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]

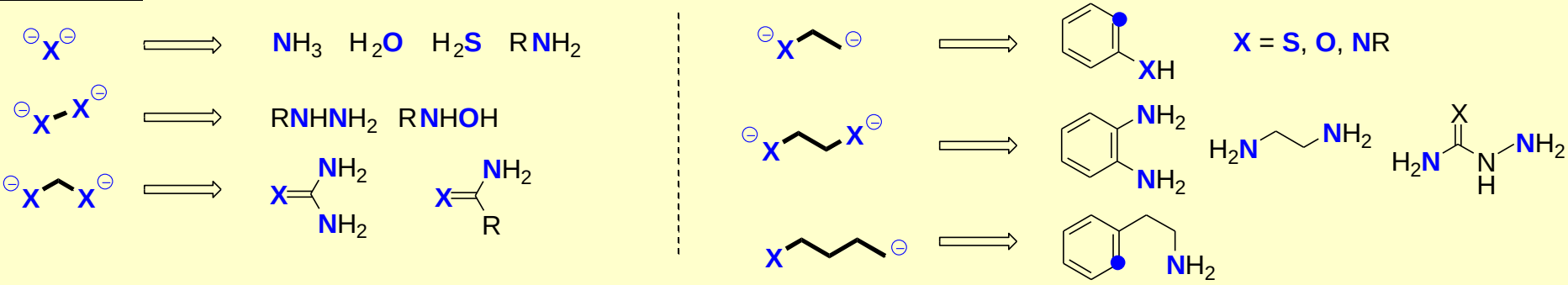


  - ***Dig*** *- electrophilic centre has sp hybridisation -* *Nucleophilic addition to nitrile/alkyne*
    - evidence for this trajectory see: Procter *Helv. Chim. Acta* **1978**, *61*, 2538 [DOI] & **1981**, *64*, 471 [DOI]

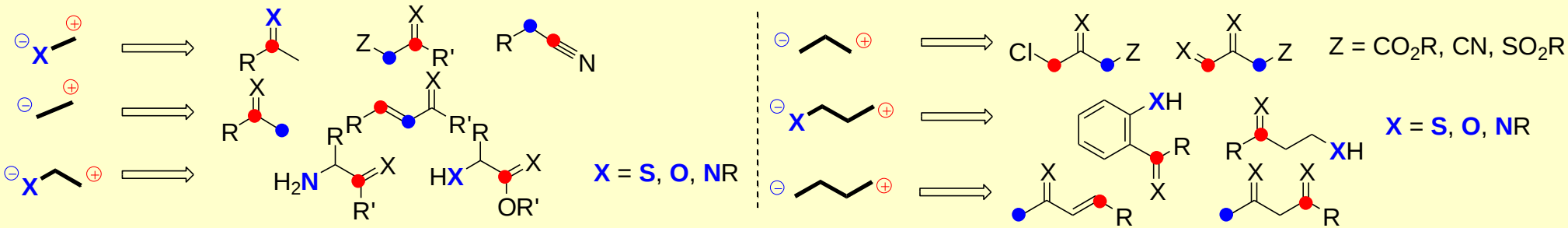


Supplementary slide 5 – *'Synthons'* ↔ Synthetic Equivalents*

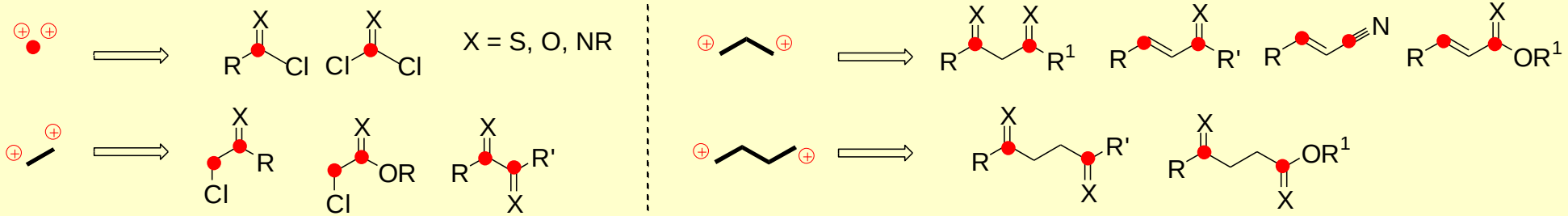
- ***dinucleophiles:***



- ***nucleophile/electrophiles:***



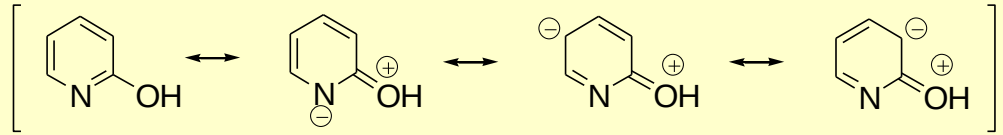
- ***dielectrophiles:***



* *The term 'synthon' is used rather loosely here to denote the indicated 'polarity assigned retrosynthetic skeleta'. For clarity and generality, these lack full indication of oxidation level unlike a true 'synthon' (see: Corey & Cheng 'The Logic of Chemical Synthesis' Wiley 1989).*

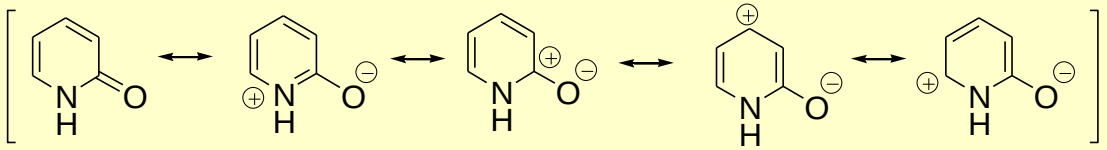
Supplementary slide 6 – *Tautomerism*

- ***Tautomerism in heterocyclic systems:***
  - many heteroaromatic compounds can exist in two or more TAUTOMERIC forms. TAUTOMERS are structurally distinct isomers in rapid equilibrium (usually). In most cases a <u>proton</u> shifts from one atom to another
  - do not confuse TAUTOMERS with resonance forms
    - *e.g.* 2-hydroxy pyridine and 2- pyridone are TAUTOMERS and are distinct isomers which can be detected spectroscopically. Each can be represented by a series of resonance structures. The position of the tautomeric equilibrium can be different in different SOLVENTS



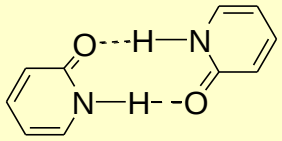
2-hydroxy pyridine

tautomeric equilibrium



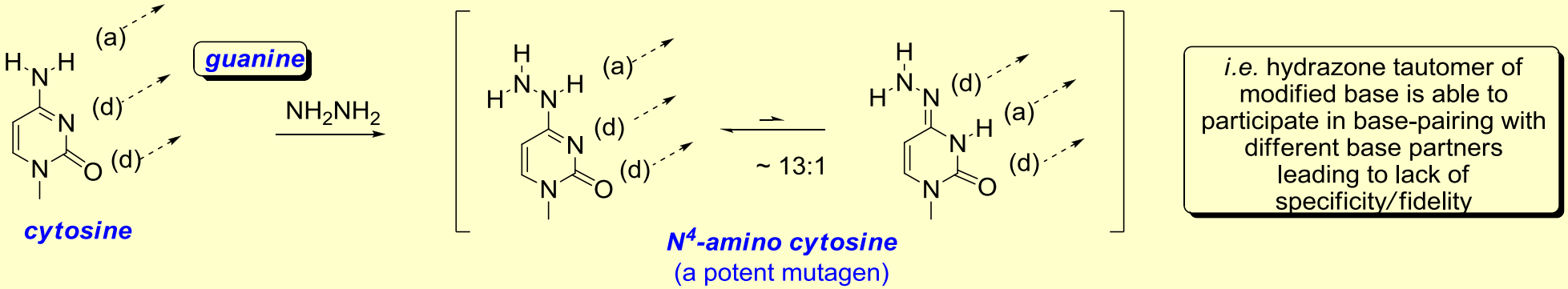
2-pyridone

  - 2-hydroxy pyridine is the predominant tautomer <u>in the gas phase</u>
  - 2-pyridone is the predominant tautomer (>9:1 in EtOH) in solution… probably due to hydrogen-bonding:



Supplementary slide 7 – *Tautomerism & Binding/Reactivity*

- ***Heterocyclic tautomerism in biological systems:***
  - tautomer specific H-bonding is important in DNA/RNA base-pairing:



- ***Tautomeric equilibria & the Curtin-Hammett principle:***
  - Curtin-Hammett principle: 'the ratio of products formed in a kinetically controlled reaction from one starting material, present in two (or more) rapidly equilibrating tautomeric forms, depends on the relative energies of the respective transition states NOT the relative ground state energies of the equilibrating tautomers.'
    - *e.g.* methylation of 2-pyridone/2-hydroxypyridine: