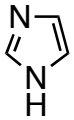
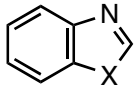
1,3-AZOLES



Imidazole

Thiazole

Oxazole

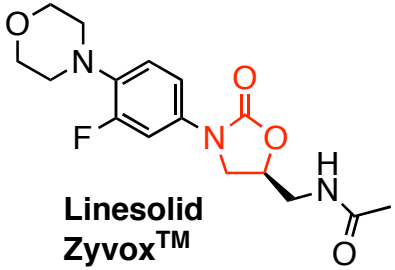


X=NH: 1*H*-Benzimidazole
X=O: Benzoxazole
X=S Benzotiazole

2-Oxazoline
(4,5-Dihydrooxazol)

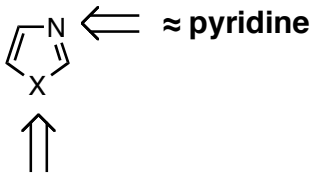
Oxazolidine

Oxazolidineone antibiotic



Linesolid
Zyvox™

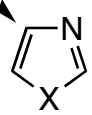
Reactivity towards E-files



≈ pyridine

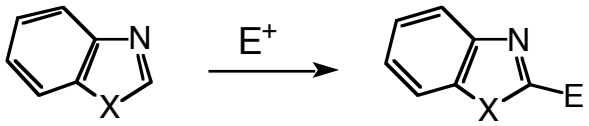
≈ pyrazole
thiophene
furan

≈C3/C4 in pyrole etc
+ inductive effect from N



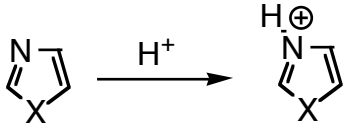
≈ C2/C6 in pyridine

≈C2/C5 in pyrole etc

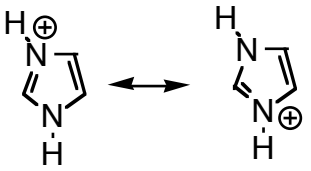


Few examples
React. generally in benzene ring

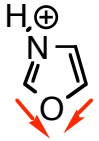
Reaction with electrophiles on N - Protonation



pKa
X=NH: 7.1
X=S: 2.5
X=O: 0.8

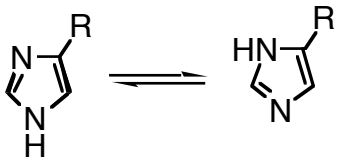


stabilized



Destabilized

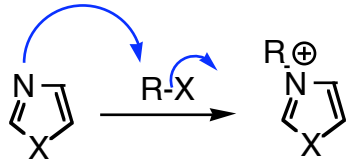
Taut.:



R= Me: ca 1 : 1
R=NO_2: ca 400 : 1

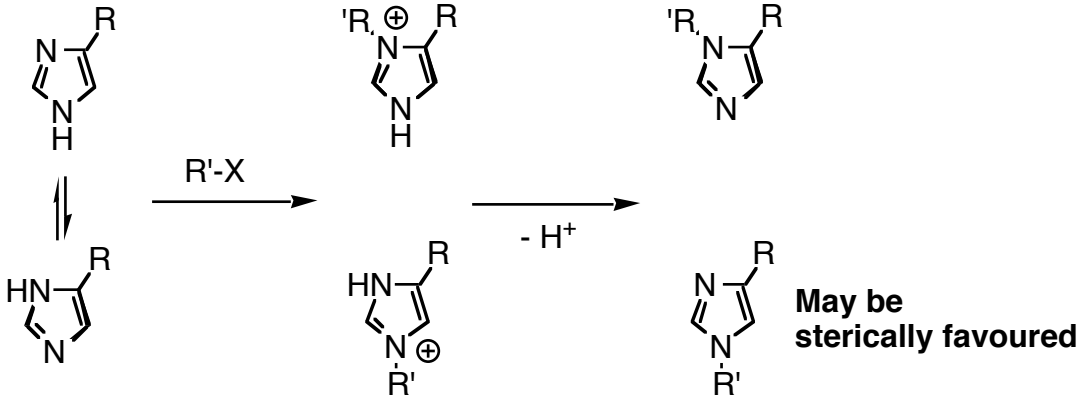
Reaction with electrophiles on N

N-Alkylation

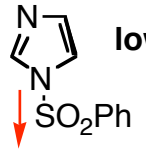


Reactivity:

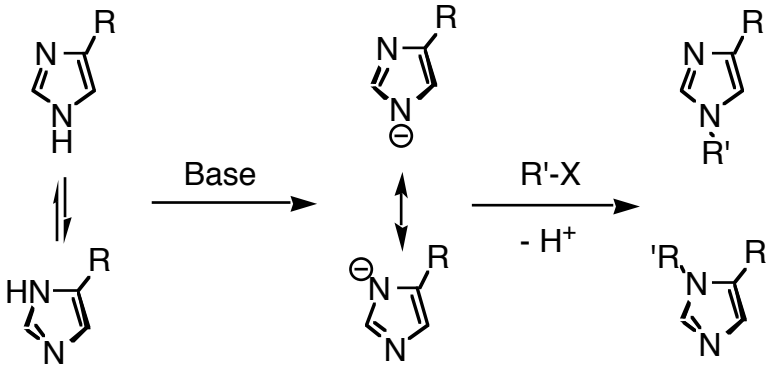
X = N-Me		X=S		X=O
900	:	15	:	1

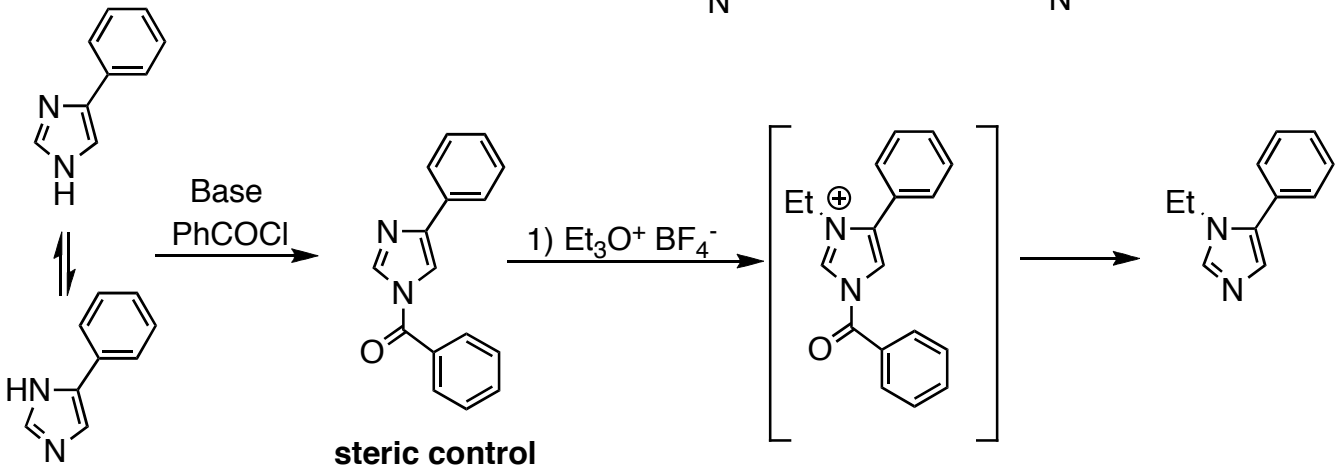


May be sterically favoured



low react.

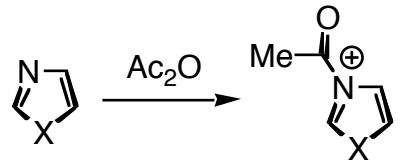




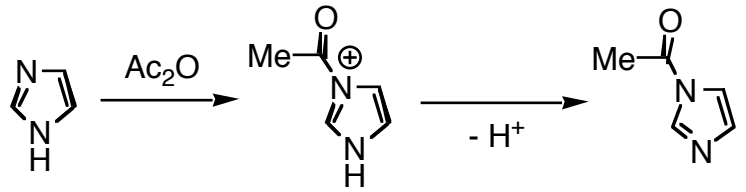
steric control

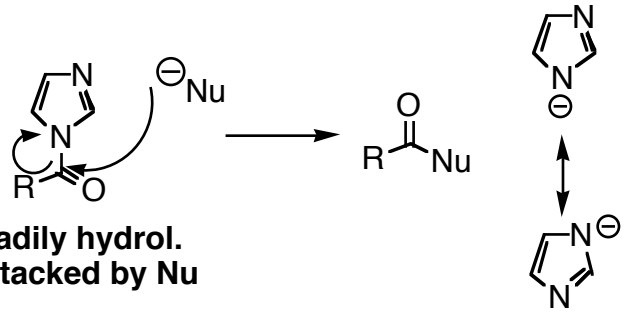
Reaction with electrophiles on N - N-Acylation

Only rel. for imidazole

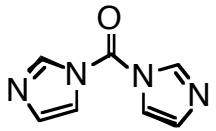


X=O, S
Unstable



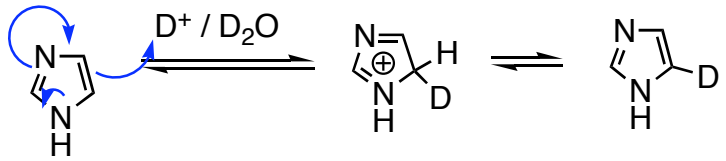


Readily hydrol.
/ attacked by Nu



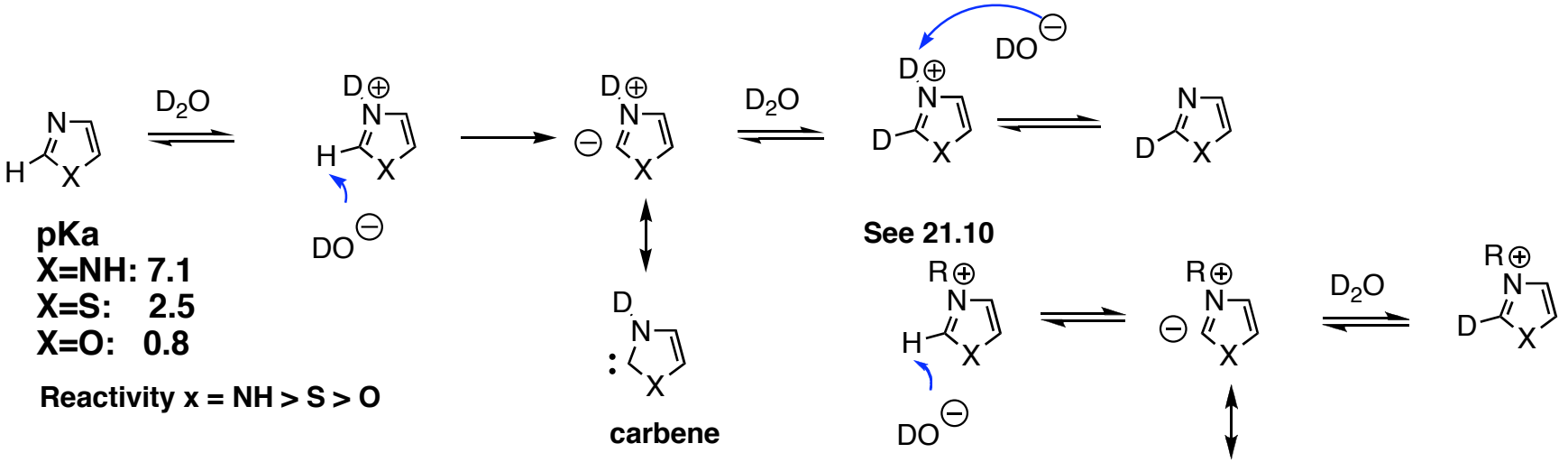
Safe equiv. of phosgene

Reaction with electrophiles on C - protonation (H / D exchange)



Slow react
Reactivity C-5 > C4 > C2

Neutral / basic cond. - Faster excange - React. in the 2-pos.



pKa
X=NH: 7.1
X=S: 2.5
X=O: 0.8

Reactivity x = NH > S > O

carbene

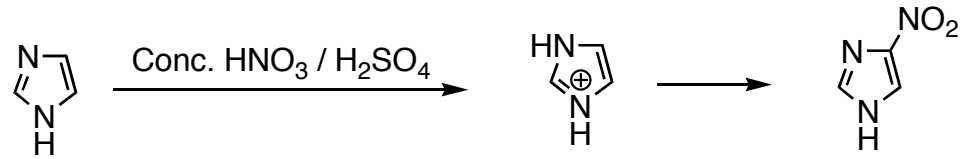
See 21.10

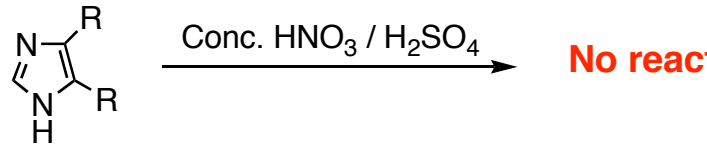
Reactivity X = O > S > NR'

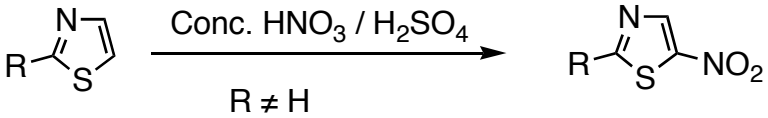
carbene

Nitration

Reactivity X = NH > S > O



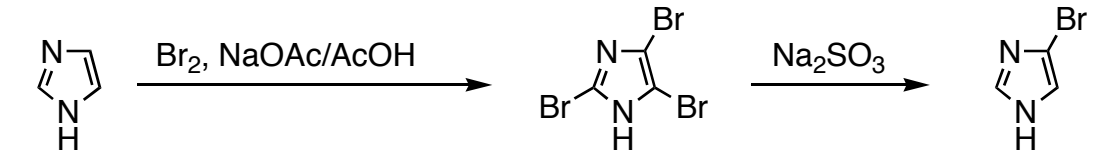


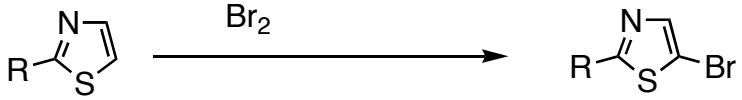


Oxazoles: No react.

Bromination

Reactivity X = NH > S > O

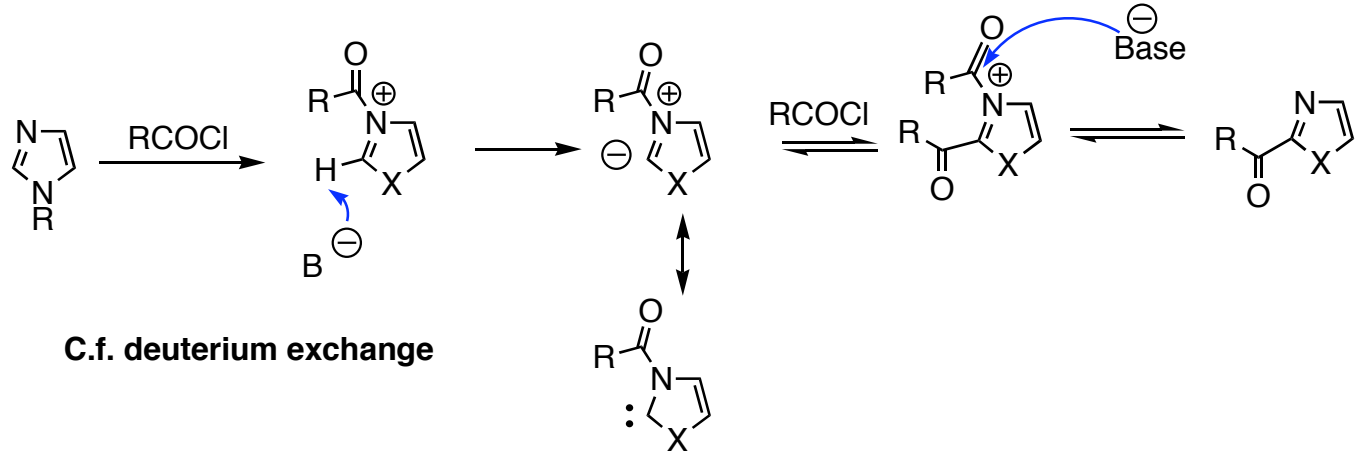




Oxazoles: No react.

Acylation

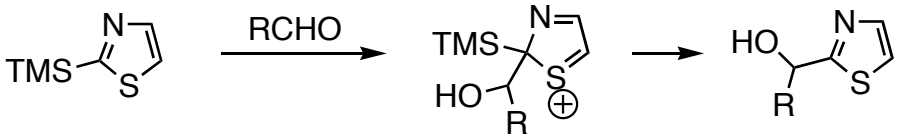
No Lewis acid cat react. (Friedel Craft, basic N)



C.f. deuterium exchange

Condensation react

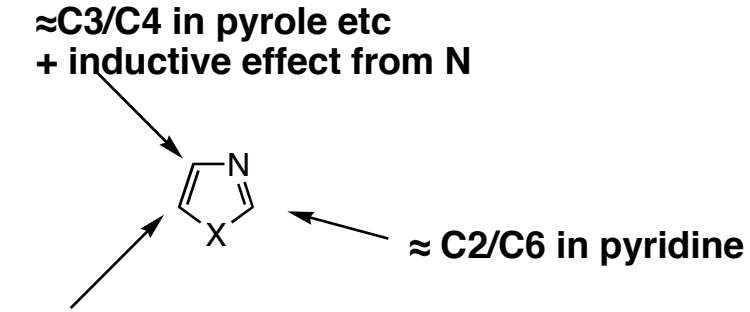
Few ex. comp. to pyrrole / thiophene / furan

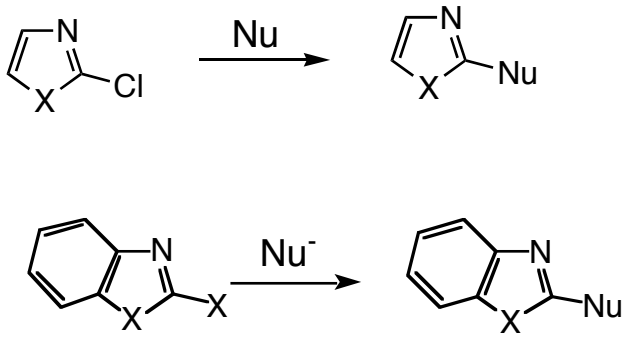


Ipso subst.

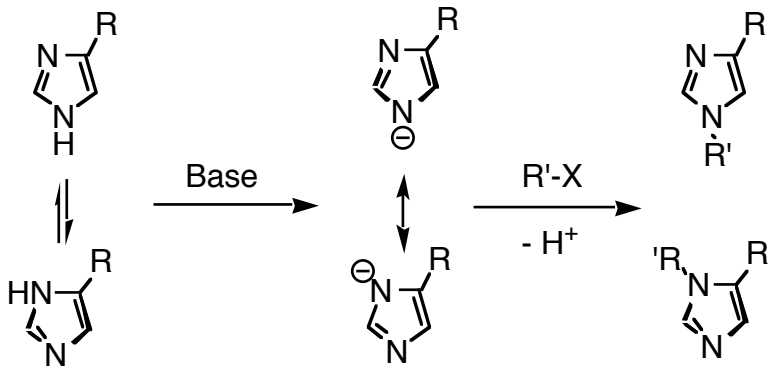
Reaction with Nucleophiles

No Nu displacement of H
Some ring opening react. on oxasole

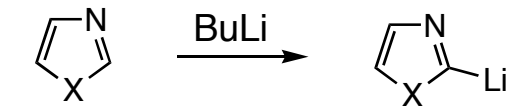




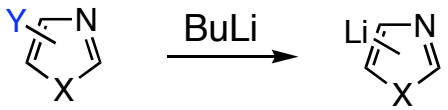
Deprotonation at N - Furter reactions



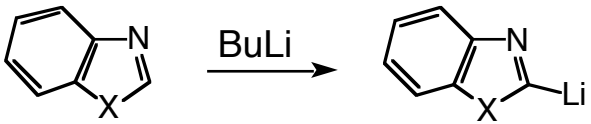
C-metallation - Furter reactions



X= NR, S

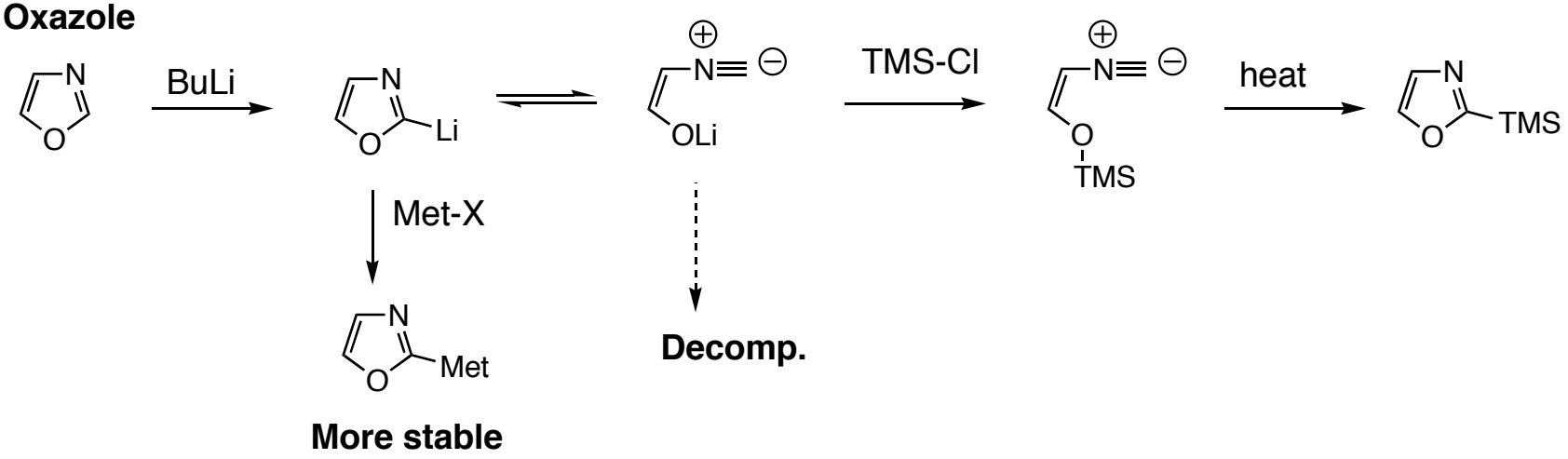


X= NR, S
Y=Br, I

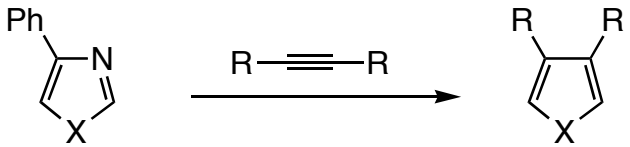


- **Transmetallation**
- **Coupling react**

Oxazole



Cycloaddition

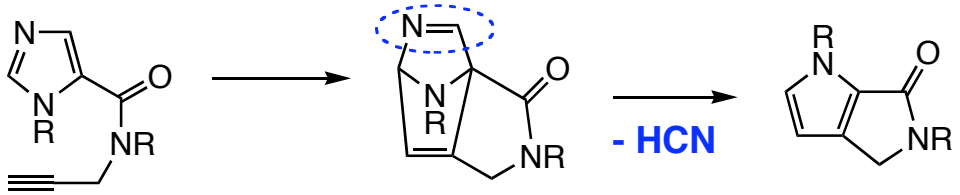


X: S, O

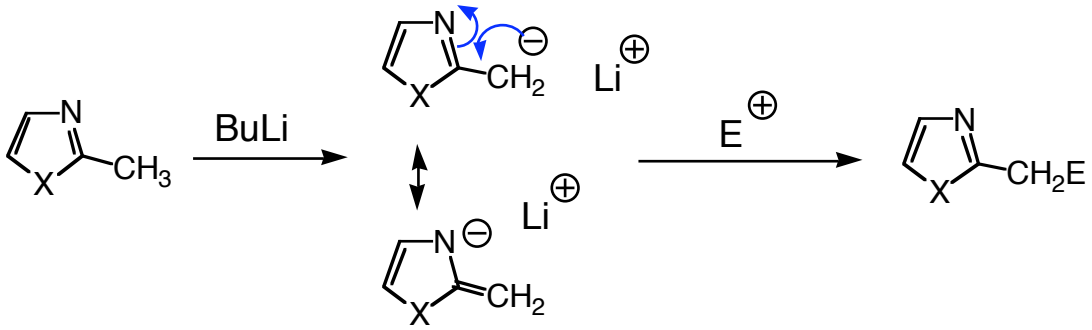
+ PhCN

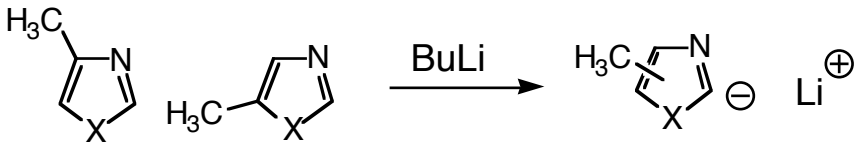
cf synth of thiophene, furan

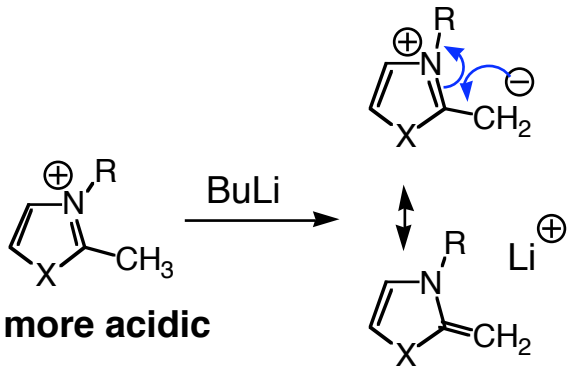
Imidazole - only intramolec. examples

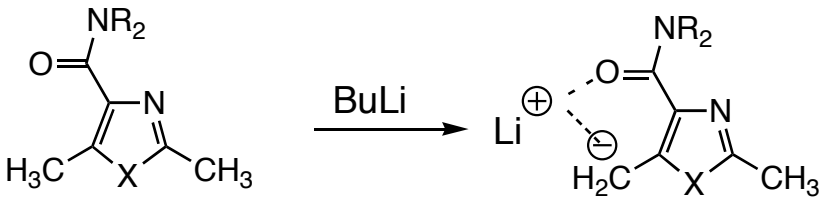


Alkylazoler



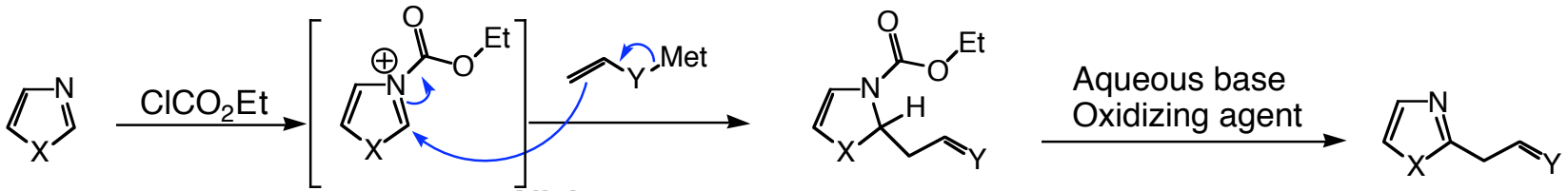






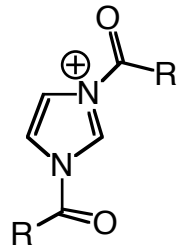
Other ODG react in 2-pos

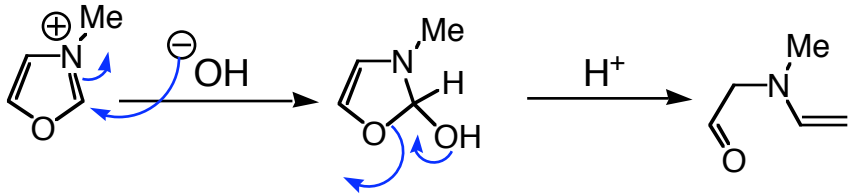
Quartenary 1,3-Diazolium Salts

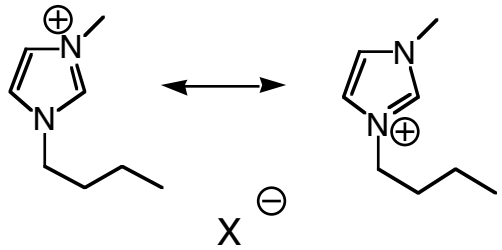


Allylstannanes
Allylsilanes
Silyl enol ethers

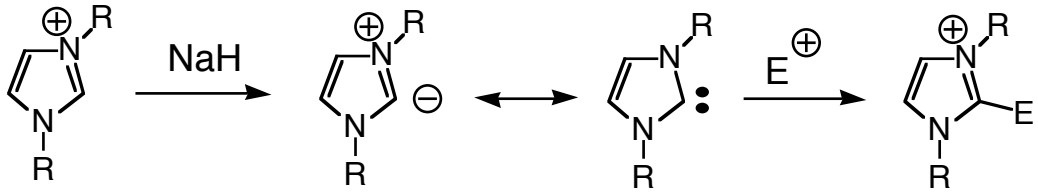
Also ring openings



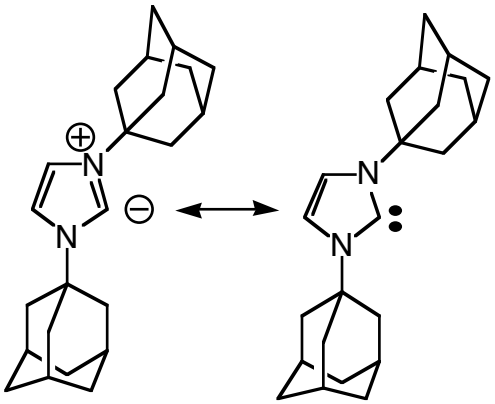


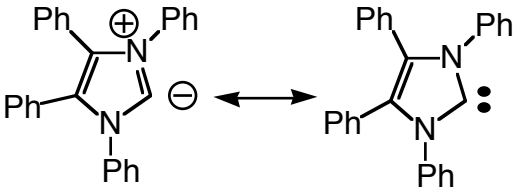


Stable compouns
Ionic liquids
(bmim)



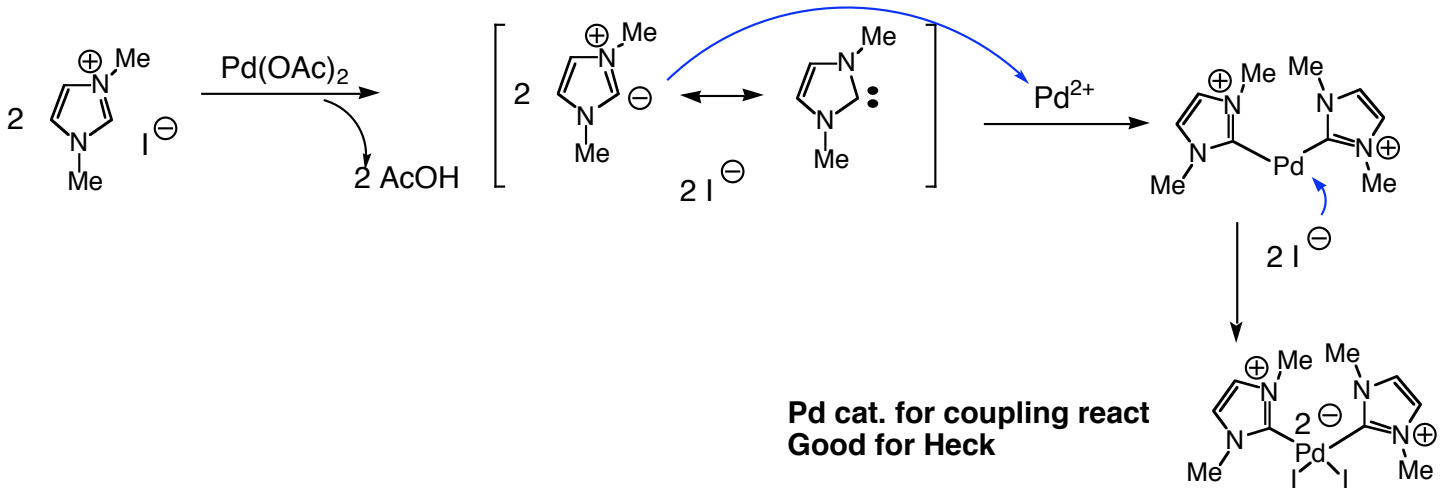
Stable crystalline compds





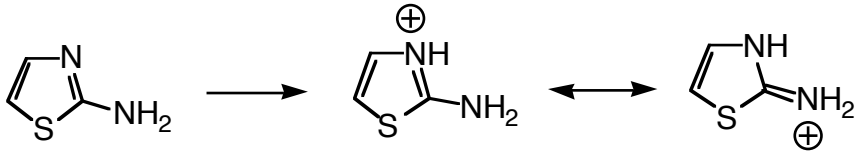
N-heterocyclic carbenes as ligands in transition metal cat react.

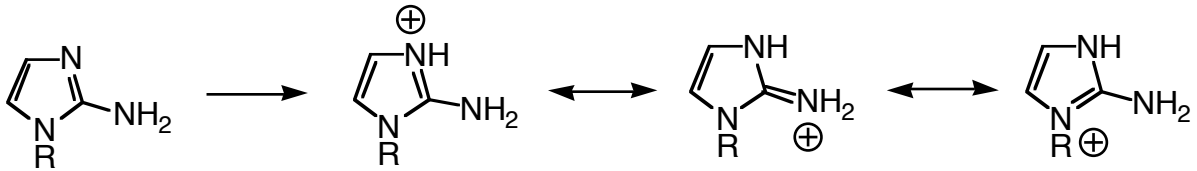
Modified properties comp. to phosphile ligands



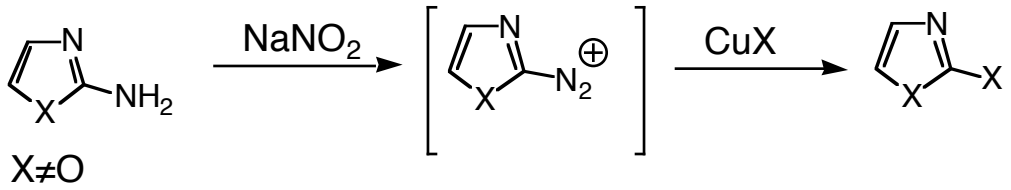
Amino 1,3-azoles

All as aminotautomers, all are protonated in the ring





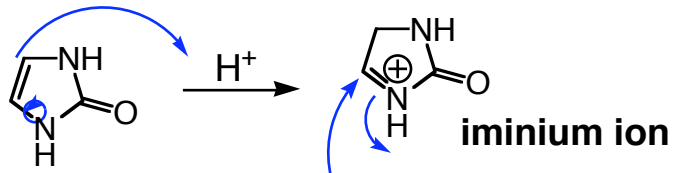
More basic (≈guanidin)



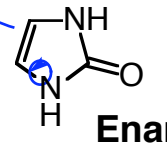
X≠O

Oxy 1,3-azoles

All as oxo (carbonyl)
Generally low aromaticity

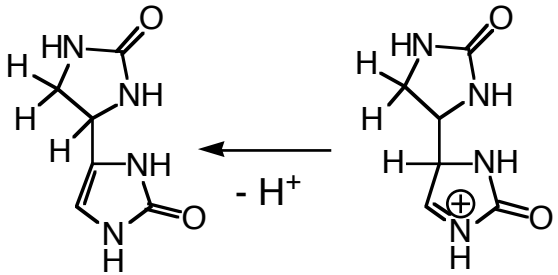


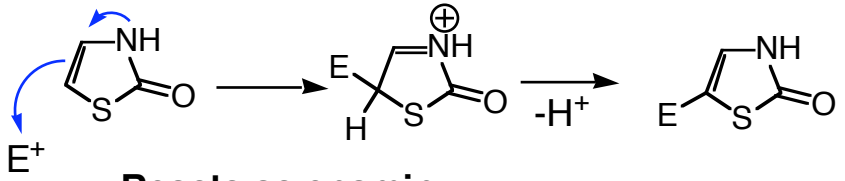
iminium ion



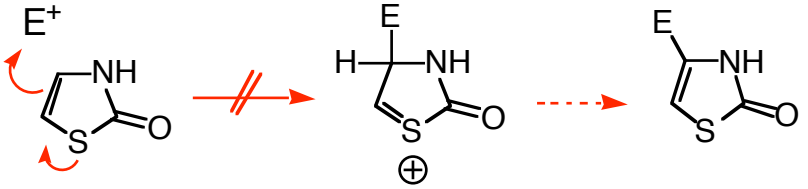
Enamin

Stable
No rearomatisation

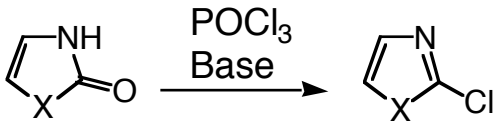




Reacts as enamin

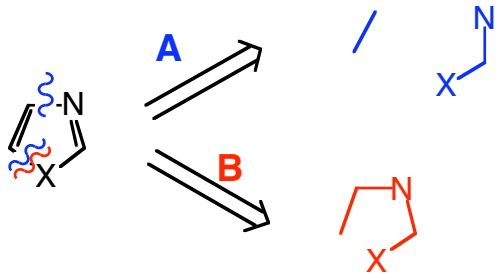


Not as thio enol ether

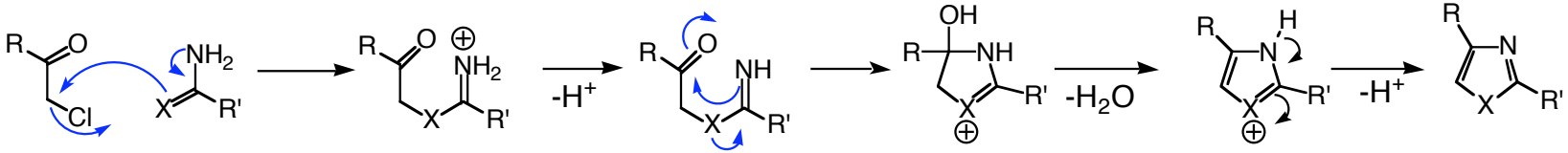


Synthesis of 1,3-azoles

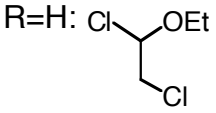
Carbonyl condensations

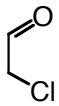


Strategy A



X=NH, O, S
R=H, Alkyl/aryl, NH_2 etc

R=H: 

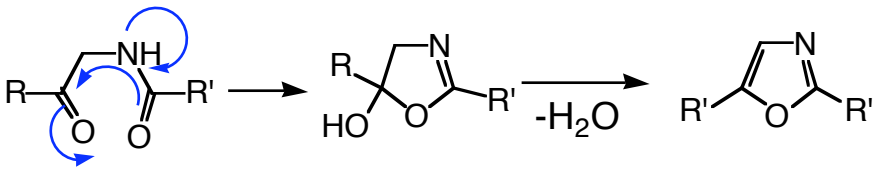
instead of 

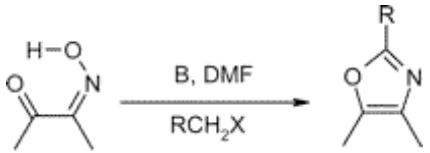
Unstable

Strategy B

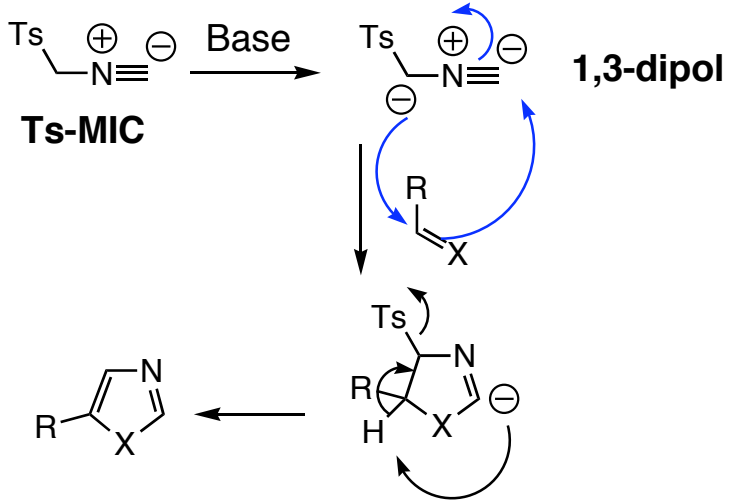
Especially valuable for oxazoles

JOC 2003, 9093

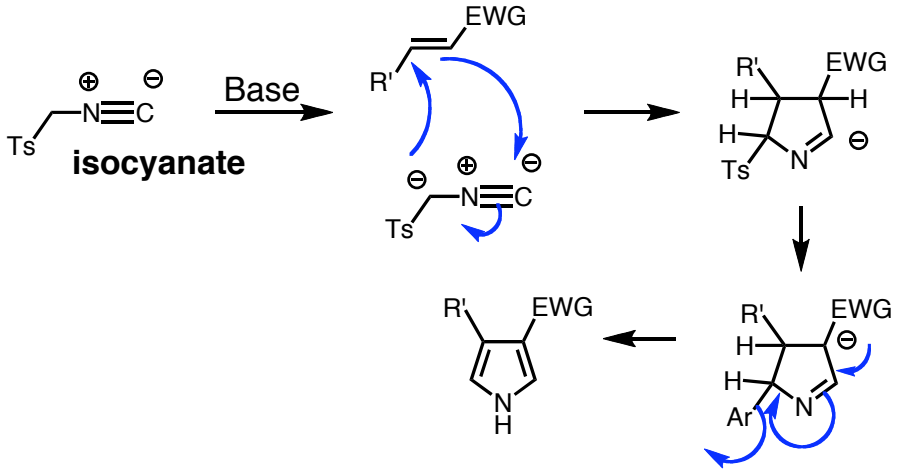


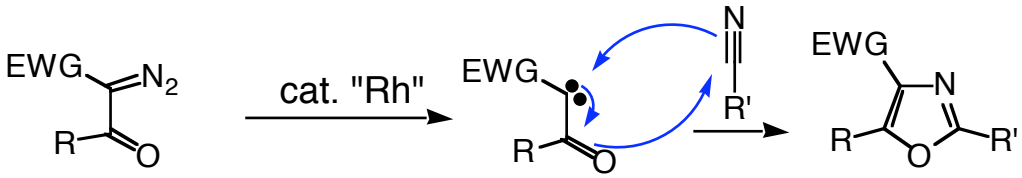


Cycloadditions



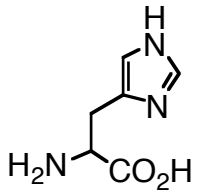
c.f. van Leusen synth. pyrrole



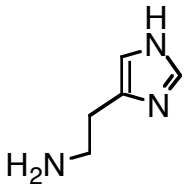


R: Alkyl/aryl (ketone) **carbenoid**
R: OR' (ester)

Bioactive 1,3-azoles

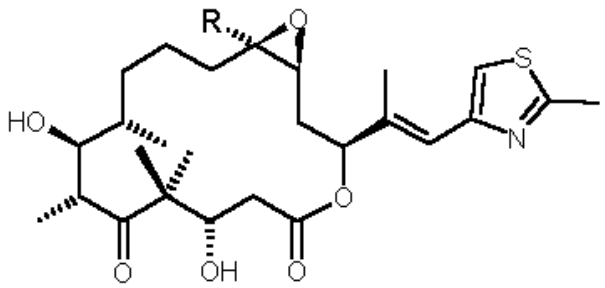


Histidine (His)



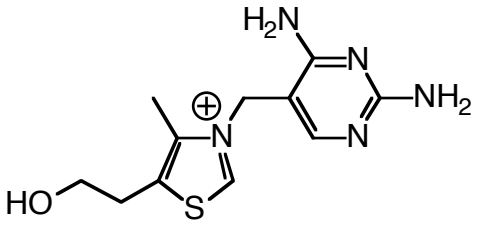
Histamine

Imidazol common in nature



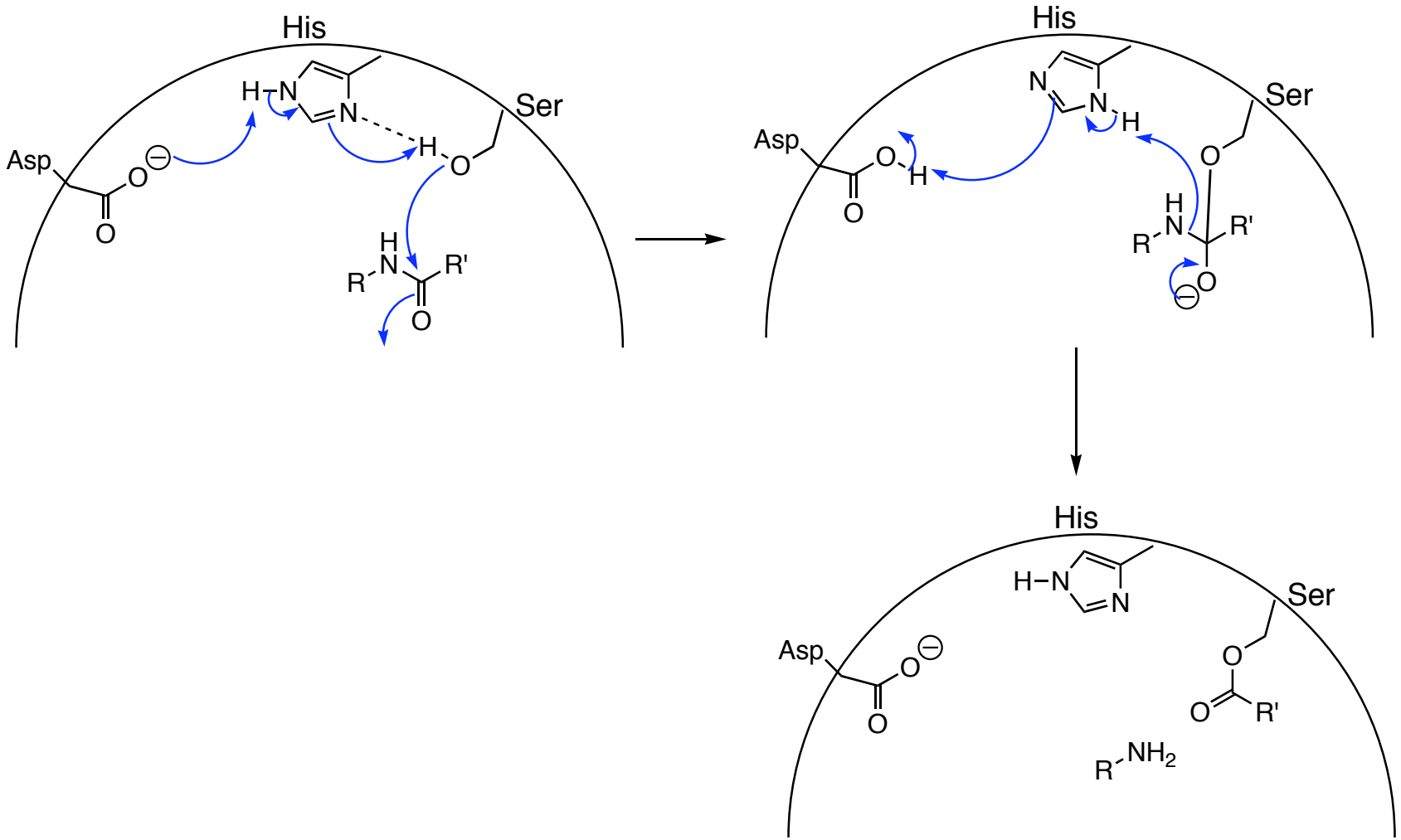
Epothilone A: R=H
Epothilone B: R=Me
From myxobacteria
Potential anticancer drugs
Mechanism ≈ taxol

Co-enzyme in biochem. prosesses:

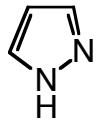


Thiamin
(Vitamin B_1)

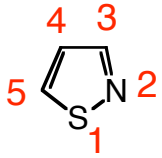
Chymotrypsin: Cleavage of peptides



1,2-AZOLES

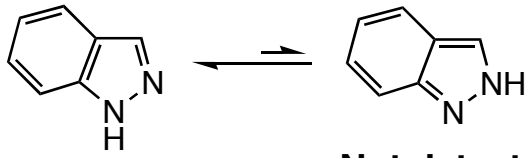


Pyrrazole



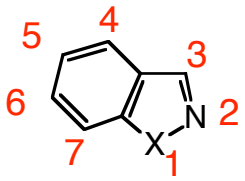
Isothiazole

Isoxazole

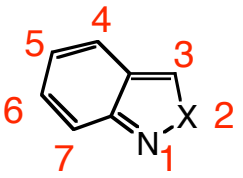


1H Benzindazol

Not detectable



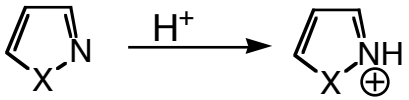
X=S: 1,2-Benzisothiazol
X=O; 1,2-Benzisoxazol

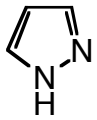


X=S: 2,1-Benzisothiazol
X=O; 2,1-Benzisoxazol
(Antranil)

Reaction with electrophiles

on N: Protonation

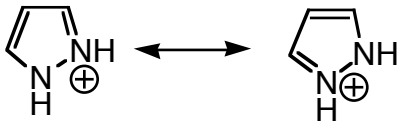


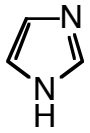


pKa 2.5

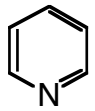
-0.5

-3.0





pKa 7.1

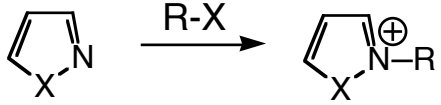


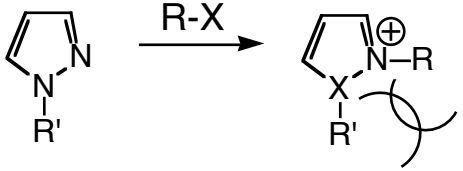
pKa 5.2

NH_3	NH_2NH_2	NH_2OH
pKa 9.3	7.9	5.8

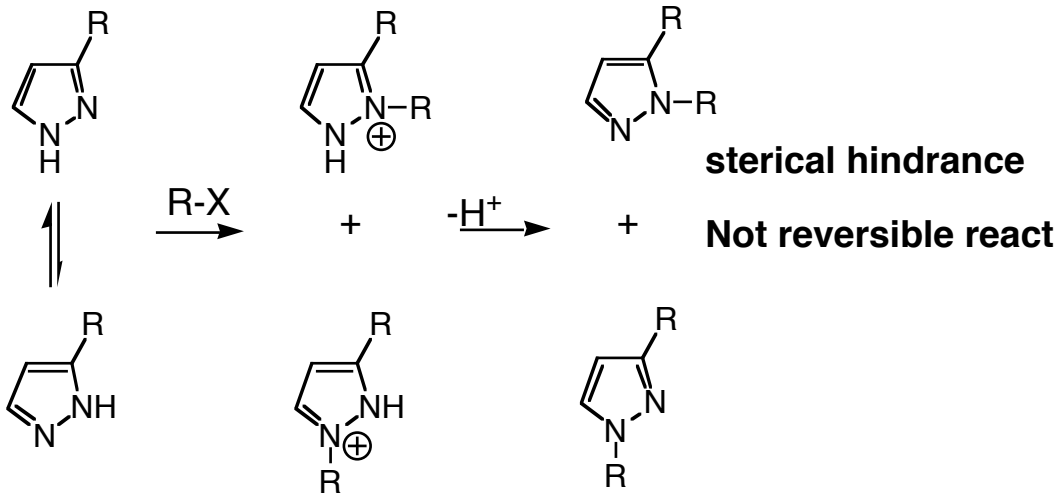
N- Alkylation and acylation

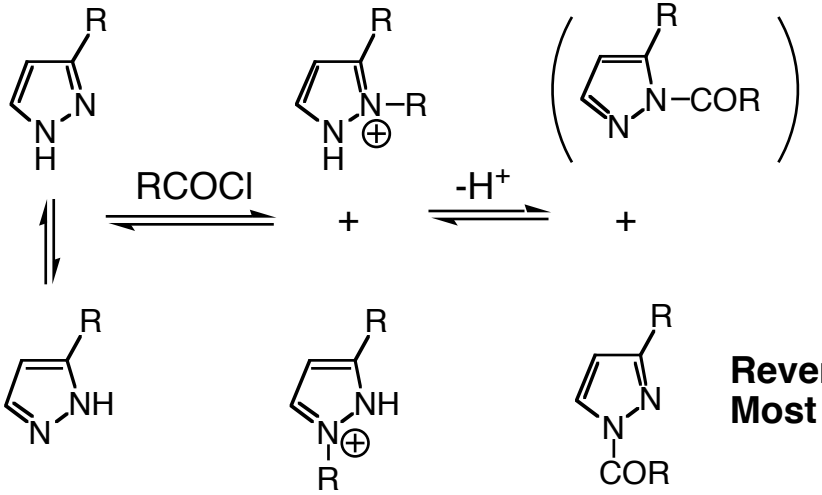
Generally more difficult than with 1,3-diazoles





X=S: Ok with reactive RX
X=O: Ring opening





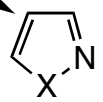
Reaction with electrophiles on C

Reactivity towards electrophiles

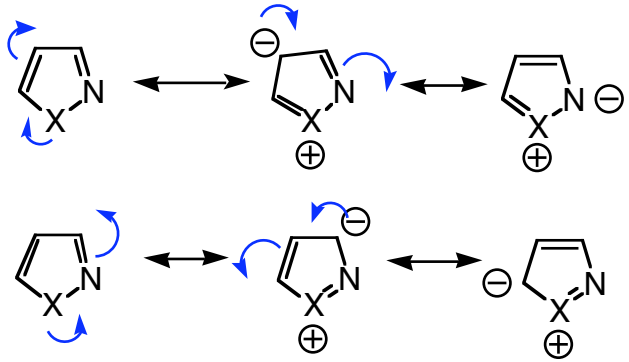
Weak deact. by N
Activated by X

Most deactivatet
(≈2-pos pyridine)

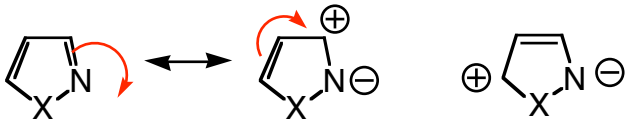
Deactivated by N
Activated by X

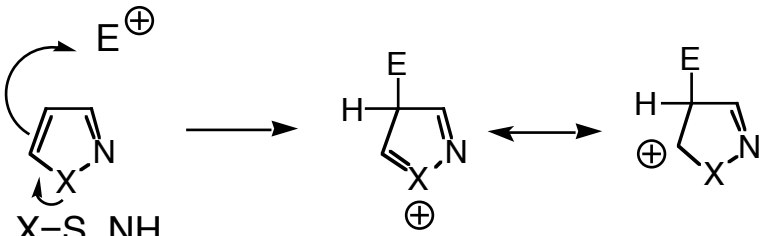


Activation by X



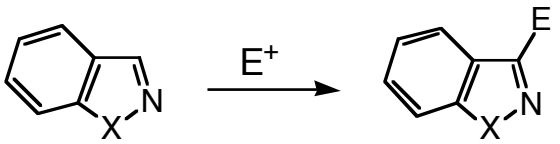
Deactivation by N





X=S, NH

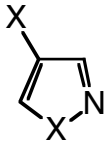
X=O: low reactivity



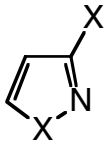
Reaction may also occur in the benzene ring

Reaction with nucleophiles

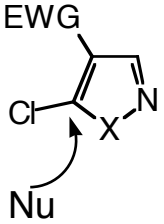
Not replacement of H



Reactivity as PhX

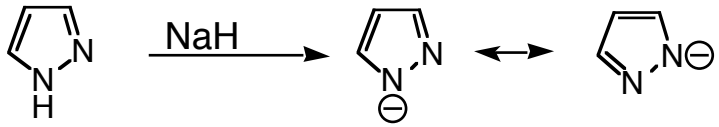


Not reactive towards Nu !?!

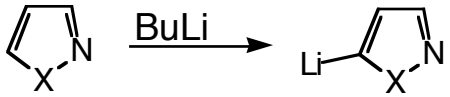


Also activated by EWG

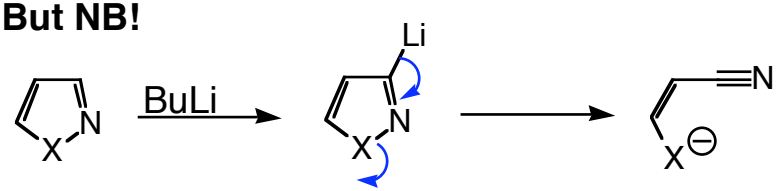
Reaction with base



pKa 14.2 (Imidazole17.5)

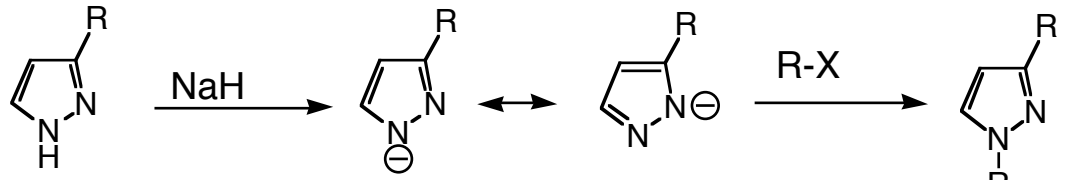


But NB!



X= O, (S)

Reaction of metallated compounds

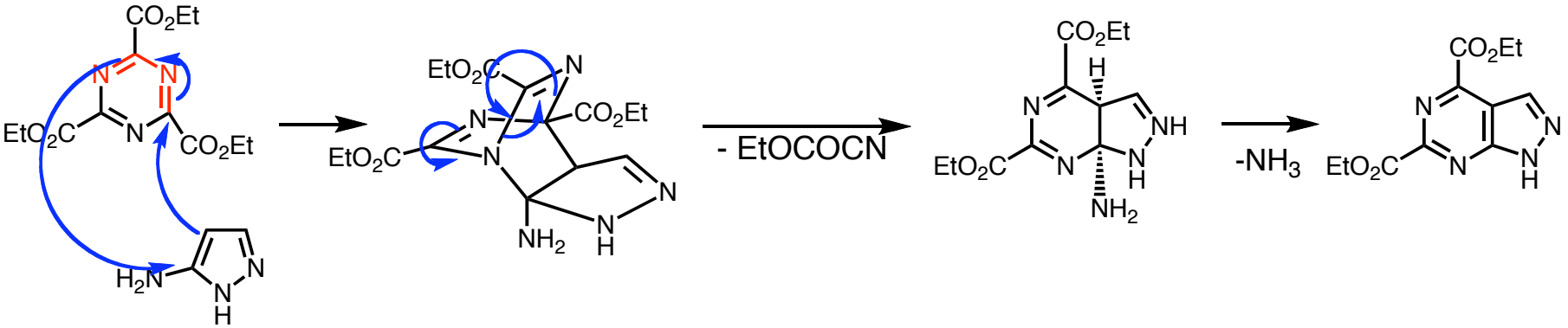


”C-Met”: Reactivity as expected

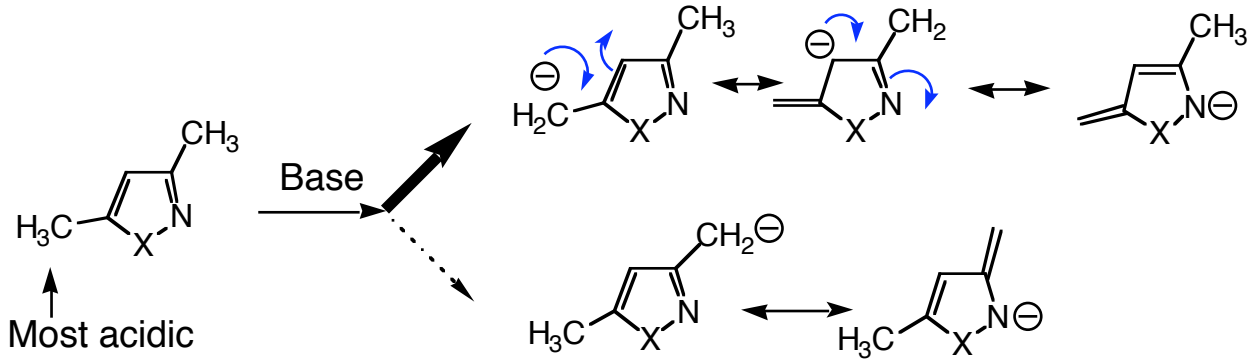
Major isomer
Sterically favoured

Cycloadditions

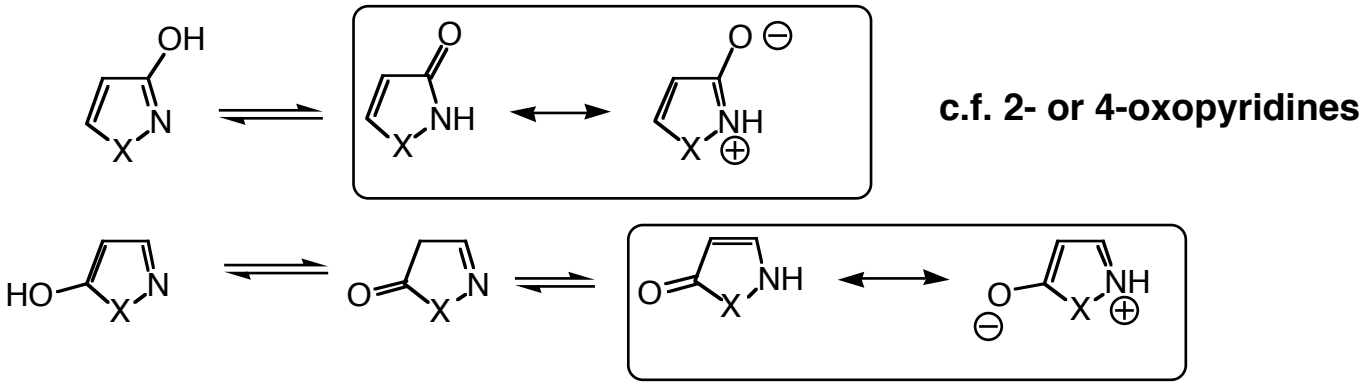
No ex. of 1,2-azoles as dienes in DA



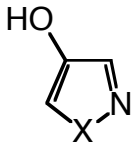
Alkyl 1,2-azoles



Oxy 1,2-diazoles



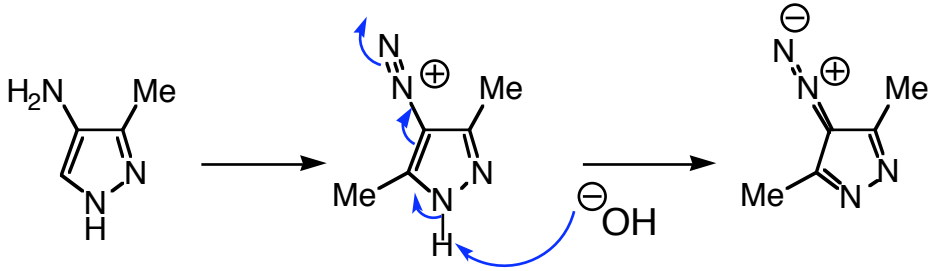
c.f. 2- or 4-oxopyridines



≈ Phenol

Amino 1,2-diazoles

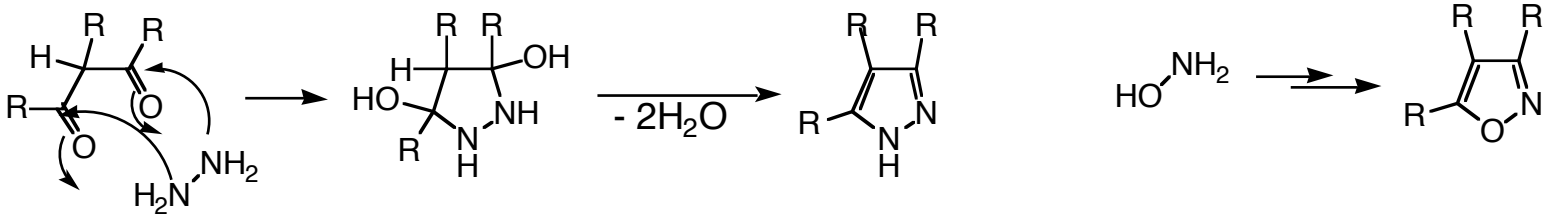
-amino form
-3 / 5-amino- ≈ anilin, diazotation etc

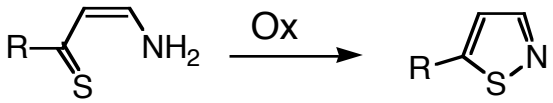


Synthesis of 1,2-azoles

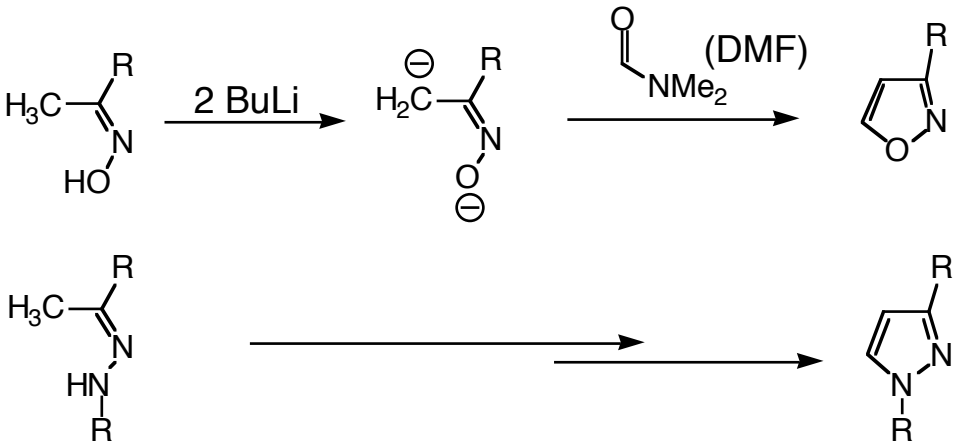
Carbonyl condensations

R: few restrict

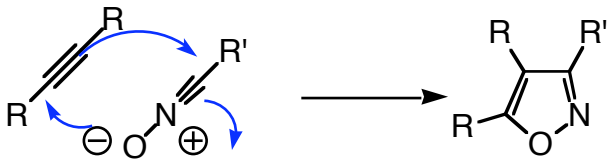




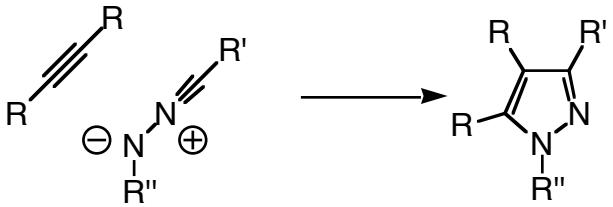
From oximes / hydrazones



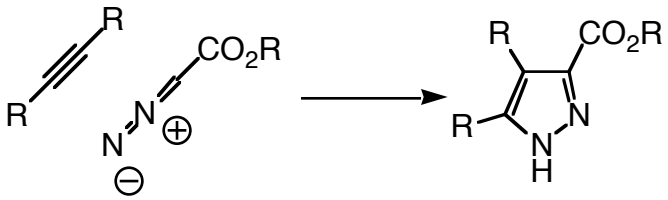
Cycloadditions



Nitril oxid



Nitril imine



Diazo