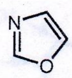
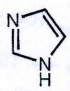
# *Synthesis and General Reactivity of Selected Heterocycles*

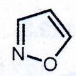
*Heresy by the Reverend Joel Austin*



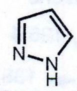

Oxazole




Imidazole




Isoxazole




Pyrazole

Lead References:
Heterocyclic Chemistry: Thomas Gilchrist
Handbook of Heterocyclic Chemistry: Alan Katritzky
ACS Short Course on Heterocyclic Chemistry
Oxazoles: Turchi
Isoxazoles part I and part II: Grunager
Imidazoles: Hofmann
Pyrazoles, Pyrazolines, Pyrazolidine, Indazoles and Condensed Rings: Wiley

---

## *What Are Heterocycles and Why Do People Care?*

- Heterocyclic compounds are those which have a cyclic structure with two, or more, different kinds of atoms in the ring.

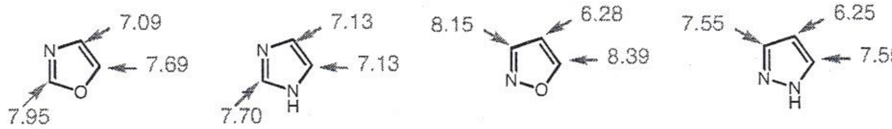
- About half of the known organic compounds have structures that incorporate at least one heterocyclic component.

- Heterocyclic compounds have a wide range of application: predominant in pharmaceuticals, agrochemicals, veternary products, dyestuffs, pigments etc.
  - Of the top 20 pharmaceuticals sold in 1994, 17 are classified as heterocycles.

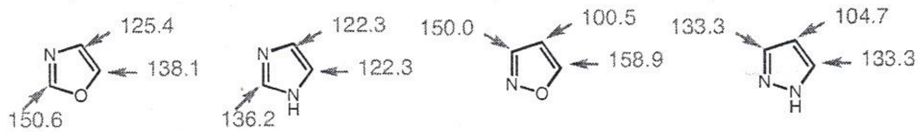
Handbook of Heterocyclic Chemistry: Alan Katritzky
Heterocyclic Chemistry: Thomas Gilchrist
Czarnik, A.W.; *Acc. Chem. Res.* **1996**, *29*, 112-113

## *Some Properties of Oxazole, Imidazole, Isoxazole and Pyrazole*

$^1H$ positions




$^{13}C$ positions

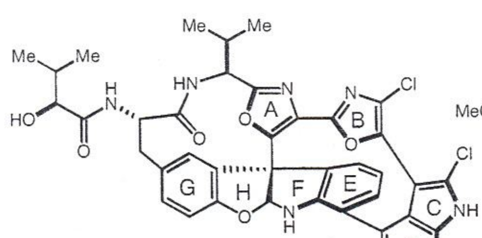



pKa Values for Proton Addition

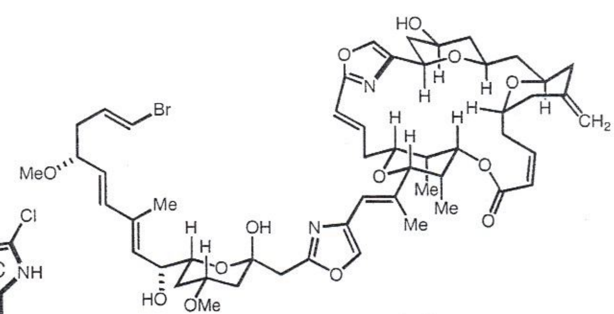

Structure determination of Organic Componds: Pretsch, Buhlmann, Affolter
Handbook of Heterocyclic Chemistry: Alan Katritzky

## *Oxazoles in Natural Products*

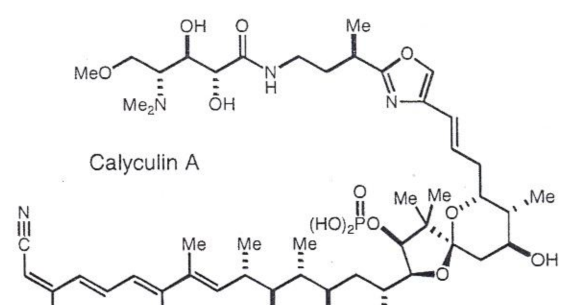
- Interest in oxazoles has increased recently due to there presence in natural products.




Diazonamide A




Phorboxazole B

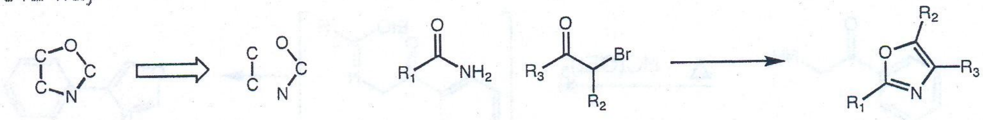



Calyculin A

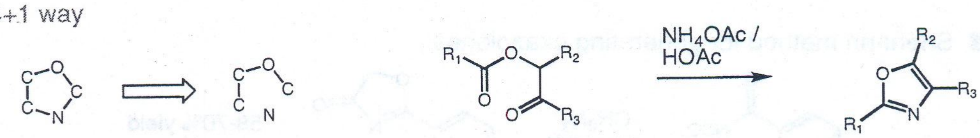
Other Natural Products Include:
Hennoxazole A
Theonezolide A
Virginiamycins
Ulapaulides
Ajudazols
Rhizoxin
Gonglobatin
Griseoviridin
Halichondramide

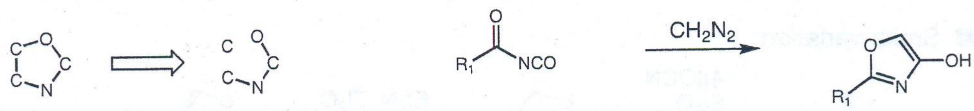
## *How to Consider the Oxazole Nucleus*

■ 3+2 way

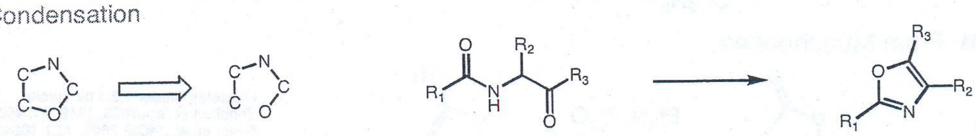


■ 4+1 way



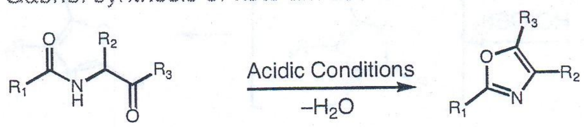




■ Condensation



## *General Approaches to Oxazoles part I*

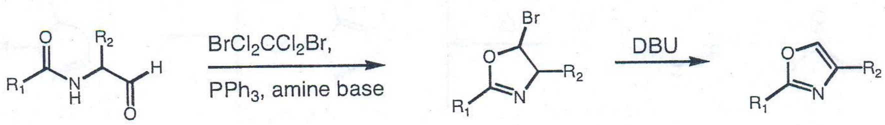
■ Robinson-Gabriel synthesis of keto amides and ester amides.



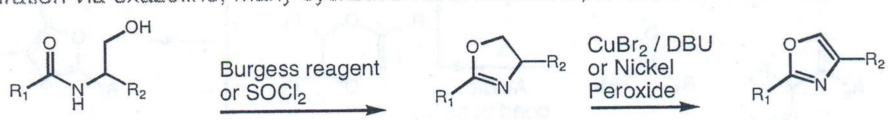

$R_{1\text{-}3}$ = Alkyl, Aryl, Heteroaryl etc.
$R_3$ can also be alkoxy, but not H

Very functional group compatable.

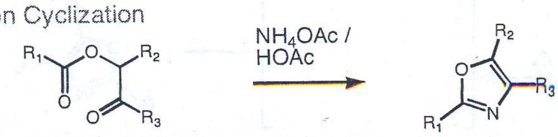
■ Wipf variation:




■ Cyclodehydration via oxazoline, many cyclization and oxidation protocols are available




■ Davidson Cyclization

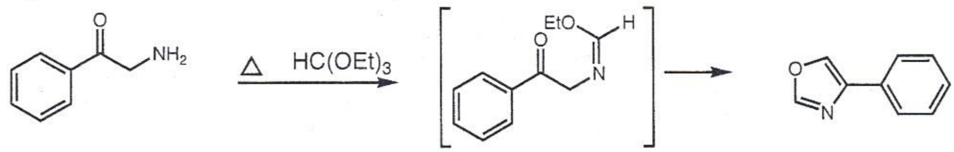



Amenable to $R_1$=H, substituted 4,5-diaryl (most common),

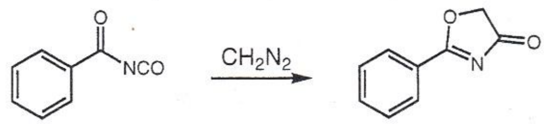
Robinson *et. al. JCS*, **1909**, *95*, 2167
Wipf *et. al. JACS*, **1995**, *117*, 558
Evans *et. al. JACS*, **1992**, *114*, 9434
Davidson *et. al. JOC*, **1937**, *2*, 328

## *General Approaches to Oxazoles part II*

- To get monosubsituted oxazoles by Robinson-Gabriel method:

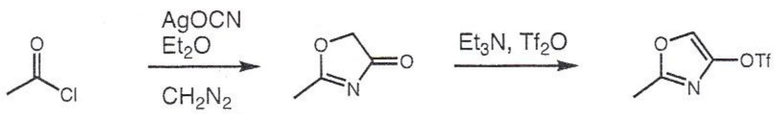



- Shehann method for generating oxazolones:

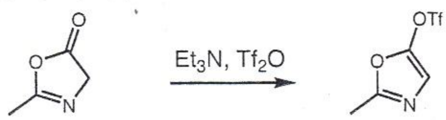



58-70% yield

- Smith variation:




- From Münchnones:

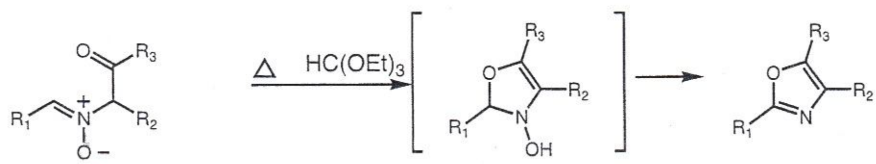



Oxazoles Chater 1.2.1 by Turchi
Sheehan *et. al. JACS*, **1949**, *71*, 4059
Smith *et. al. JACS*, **2001**, *123*, 10942

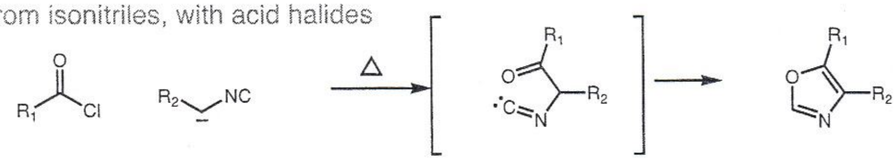
---

## *Less General Approaches to Oxazoles*

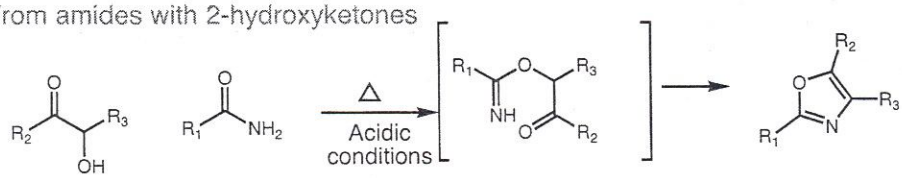
- From 2-ketonitrones



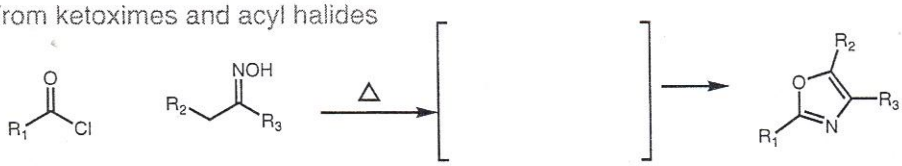

- From isonitriles, with acid halides




- From amides with 2-hydroxyketones



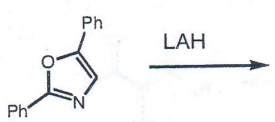

- From ketoximes and acyl halides



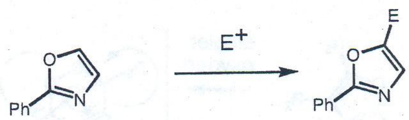

Oxazoles Chater 1.2 by Turchi

## General Reactivity of Oxazoles

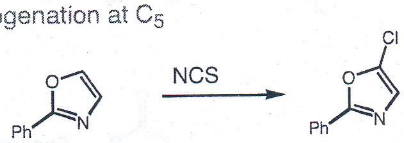
- Reduction with LAH



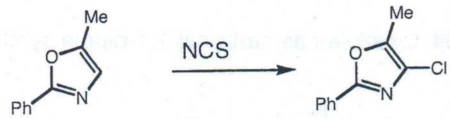

- Electrophilic attack at $C_5$




- Halogenation at $C_5$

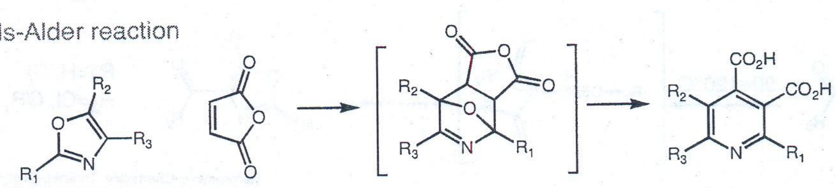



- Halogenation at $C_4$




- Hydrogenation

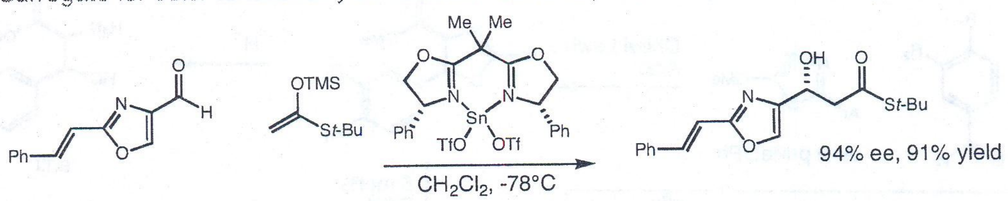

- Diels-Alder reaction



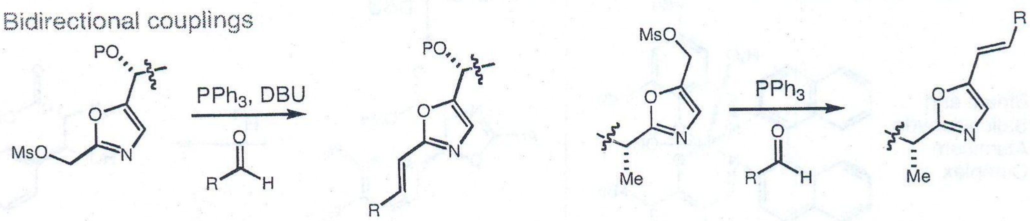
Handbook of Heterocyclic Chemistry: Alan Katritzky

## Fun with Oxazoles

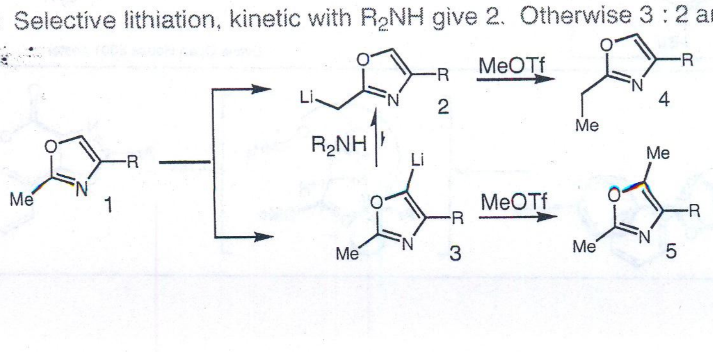
- Surrogate for ester functionality in medicinal chemistry and... asymmetric catalysis




- Bidirectional couplings



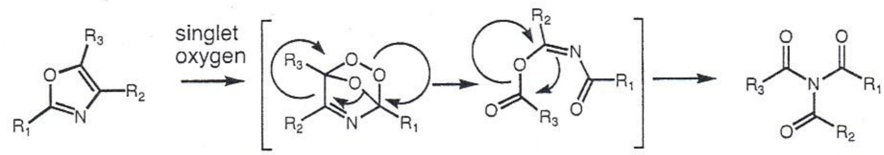

- Selective lithiation, kinetic with $R_2NH$ give 2. Otherwise 3 : 2 are roughly equal.



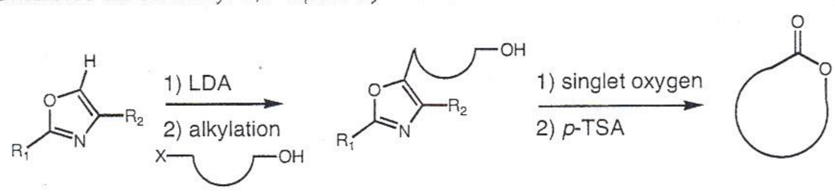

Evans *et. al. JACS*, **2000**, *122*, 10033
Evans *et. al. JACS*, **1992**, *114*, 9434
Evans *et. al. Org. Lett.*, **1999**, *1*, 87

# *More Fun with Oxazoles*

- The Chapman reaction

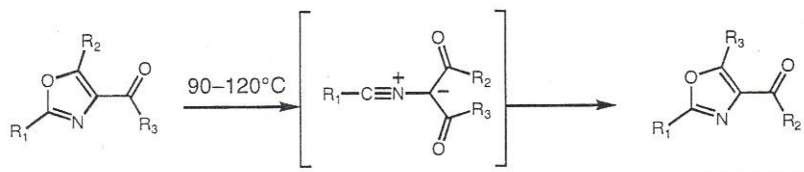



- Oxazoles as carbonyl 1,1-dipole synthons




Examples with 5, 8, 10, and 12 membered rings

- The Cornforth rearrangment

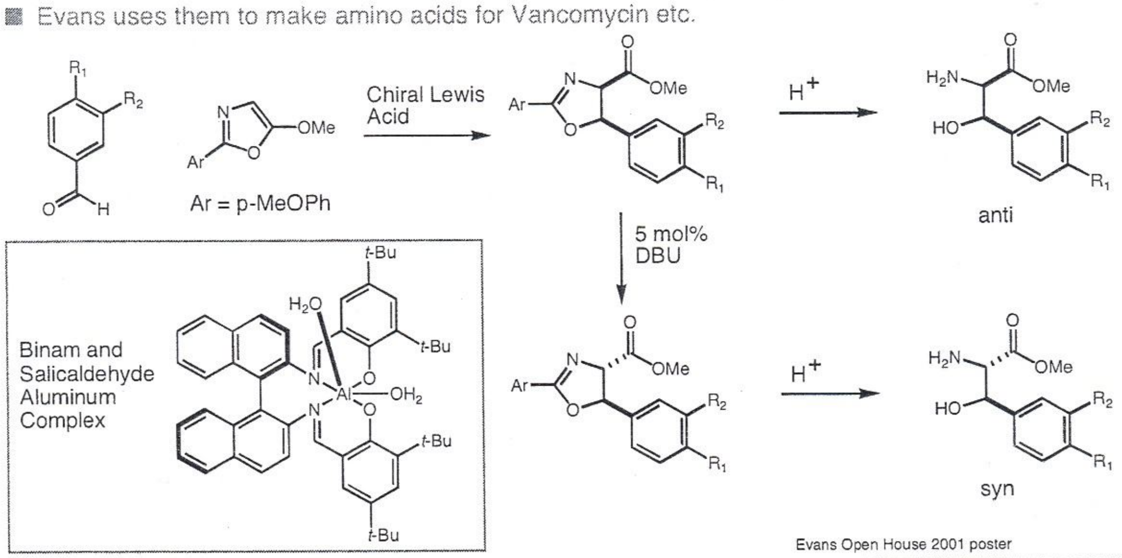



$R_3$=H, Cl
$R_2$=Cl, OR, $O^-$

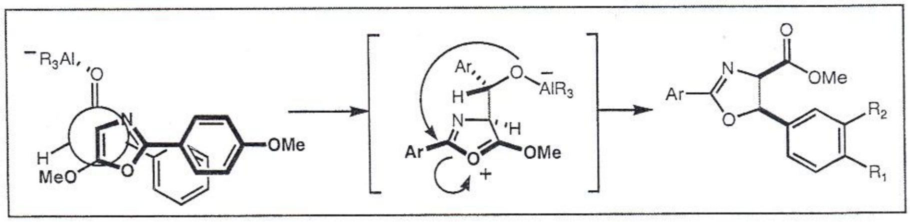
Heterocyclic Chemistry: Thomas Gilchrist
ACS Short Course on Heterocyclic Chemistry
Oxazoles: Turchi

# *And More Fun with Oxazoles*

- Evans uses them to make amino acids for Vancomycin etc.

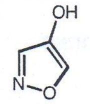


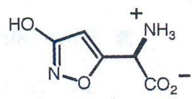

Evans Open House 2001 poster

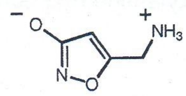


# *Isoxazoles are NOT Prevalent in Natural Products*

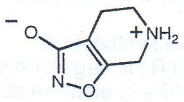
- Interest in isoxazoles is not due to natural products

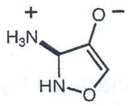

Triumferol

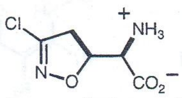

Ibotenic acid


Muscimol

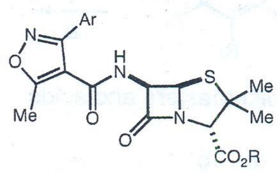
- Interest in isoxazoles is more directed towards there synthetic utility and pharmacology


Synthetic isoxazoles as potent analgesics


Cycloserine is an antituberculosis antibiotics


Isoxazoline as antitumor antibiotic

Synthetic penicillin derivatives

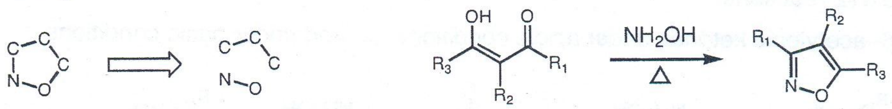


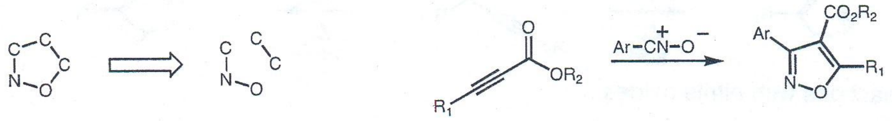
| | Ar | R |
|---|---|---|
| Oxacillin | Ph | Na |
| Cloxacillin | 2-ClPh | Me |
| Dicloxacillin | 2,6-$Cl_2$Ph | Me |
| Flucloxacillin | 2-Cl, 6-FPh | Me |

Heterocyclic Chemistry: Thomas Gilchrist
Isoxazoles part I and part II: Grunager

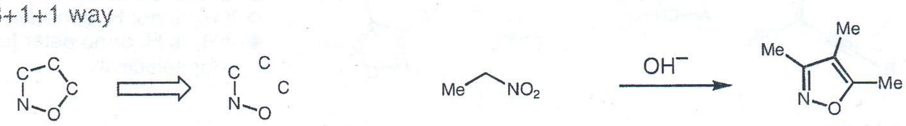
# *How to Consider the Isoxazole Nucleus*

- 3+2 way

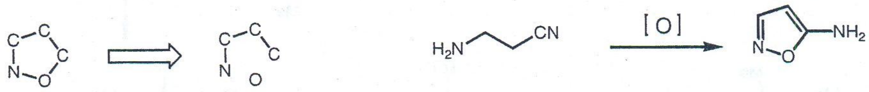


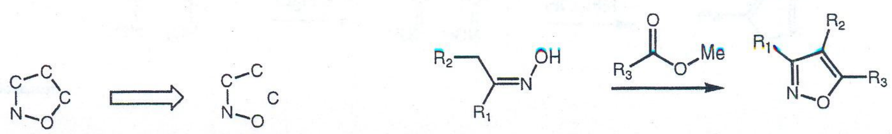




- 3+1+1 way



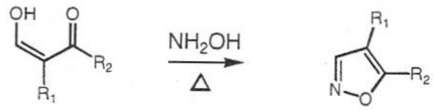

- 4+1 way



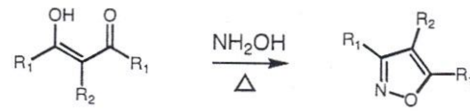



## *General Approaches to Isoxazoles part I*

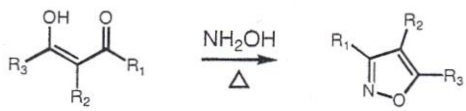
- 3+2 way (with hydroxylamine hydrochloride)
  - Aldehydes




  - Symmetrical ketones

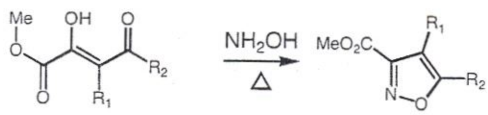



  - Unsymmetrical ketones: $R_1$ and $R_3$ must be very different, or isomeric isoxaxoles formed



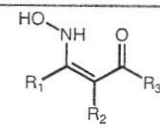

Selective isoxazole synthesis if:
- $R_1$ is small and $R_3$ is large or aryl
- $R_1$ is large and $R_3$ is electron rich aryl
- $R_1$ is aryl and $R_3$ is large, conjugated aryl or electron rich aryl

  - β–diketoesters and acids




- Isomer is enforced the larger $R_2$ becomes

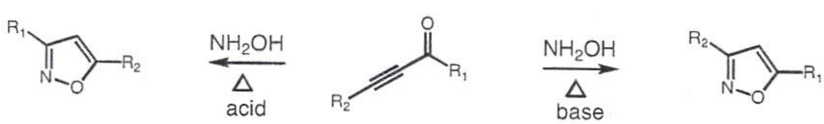
β–monoxime intermediate can be isolated in some cases



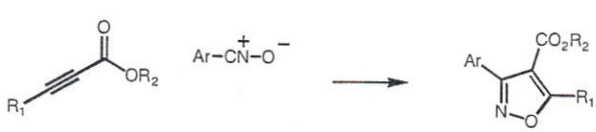



## *General Approaches to Isoxazoles part II*

- More 3+2 reactions
  - α,β–acetylenic ketones under acidic conditions...... and under basic conditions.

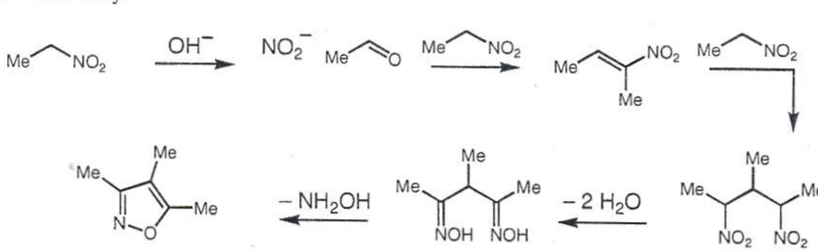



  - Reactions with nitrile oxides...




Selective isoxazole synthesis if:
- If $R_1$ is not H, generally very selective.
- If $R_1$ is H, or no ester functionality, then poor selectivity.

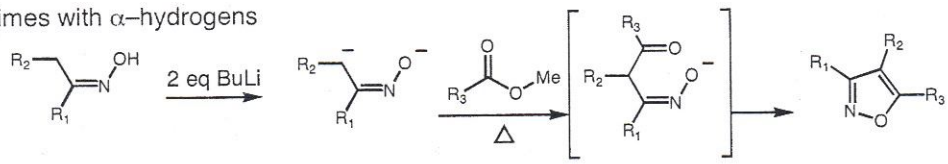
- 3+1+1 way



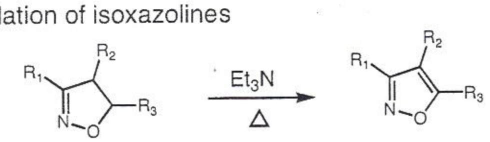

Isoxazoles part I: Grunager

## *General Approaches to Isoxazoles part III*

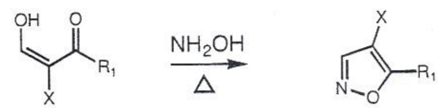
- 4+1 way
  - Oximes with α–hydrogens




- Miscellaneous
  - Oxidation of isoxazolines



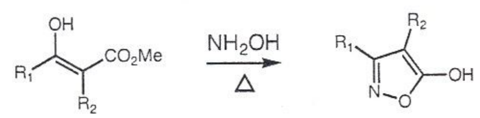

  - Heteroatoms at $C_4$




X=OP, SP, NP

  - β-Ketonitriles


  - β-Ketoesters

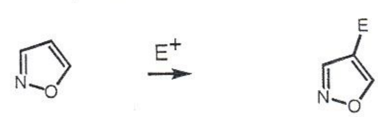



Isoxazoles part I: Grunager

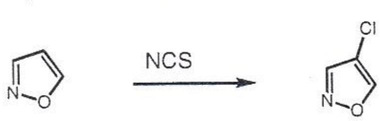
## *General Reactivity of Isoxazoles*

- Reaction with strong reducing agents (LAH, Stannous Chloride, Zinc dust / acetic acid, etc.) do not affect this ring system unless "special" substitution patterns.

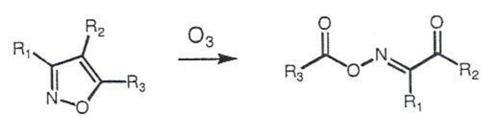
- Electrophilic attack at $C_4$




- Halogenation at $C_4$

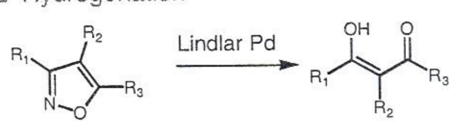



- Ozonolysis

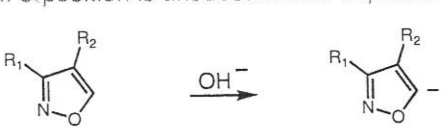



- Hydrogenation


- Hydrogenation



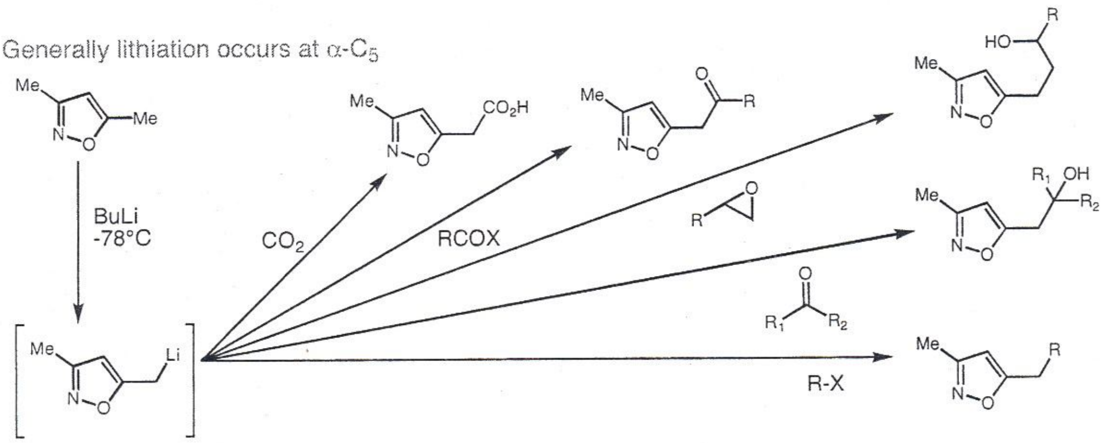

- If 5-position is unsubstituted... deprotonated easily.




Isoxazoles part I: Grunager
Handbook of Heterocyclic Chemistry: Alan Katritzky

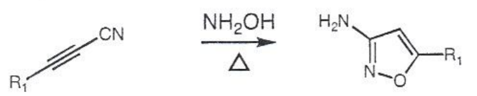
# *Fun with Isoxazoles*

- Generally lithiation occurs at $\alpha$-$C_5$

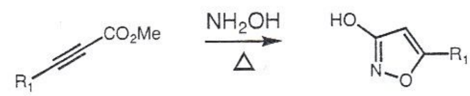



- Placement of heteroatoms at $C_3$

  - $\beta$-Ketonitriles



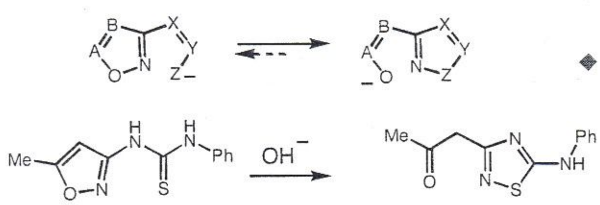

  - $\beta$-Ketoesters




Heterocyclic Chemistry: Thomas Gilchrist
Isoxazoles part I: Grunager

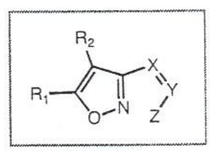
# *More Fun with Isoxazoles Using the Boulton-Katritzky Rearangement*

- Boulton-Katritzky rearrangment

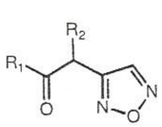



◆ XYZ=NCS
1,2,4-Thiadiazole

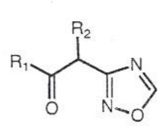
◆ General rearrangment for 5-membered heterocycles that contain an N—O bond.
◆ As long as Z is not O, rearrangment is not reversible.
◆ Thermal or base promoted process.



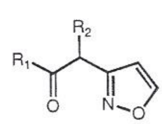
Heterocyclic Chemistry: Thomas Gilchrist
Isoxazoles part I: Grunager
Ruccia *et. al. Adv. Het. Chem.*, **1981**, *29*, 141
Vivona *et. al. Adv. Het. Chem.*, **1993**, *56*, 49



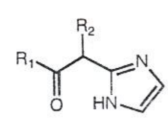
◆ XYZ=CNO
1,2,5-Oxadiazole



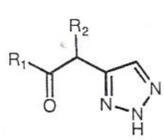
◆ XYZ=NCO
1,2,4-Oxadiazole



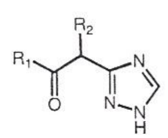
◆ XYZ=CCO
Isoxazole



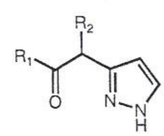
◆ XYZ=NCC
Imidazole



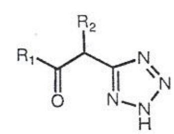
◆ XYZ=CNN
1,2,3-Triazole



◆ XYZ=NCN
1,2,4-Triazole



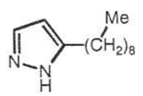
◆ XYZ=CCN
Pyrazole

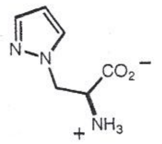


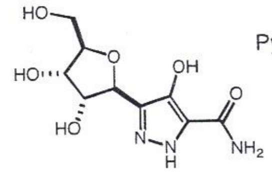
◆ XYZ=NNN
Tetrazole

## *Pyrazoles are also NOT Prevalent in Natural Products*

- Only three natural product isolates have the pyrazole nucleus

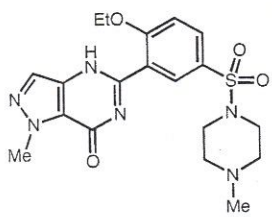




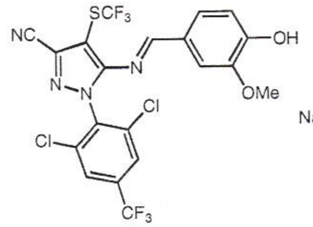


Pyrazomycin

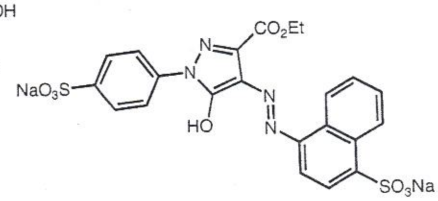
- Pyrazoles have been incorporated in many pharmacuticals, insecticides, and dyes



Sildenafil



Vaniliprole



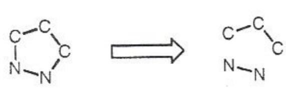
Orange B

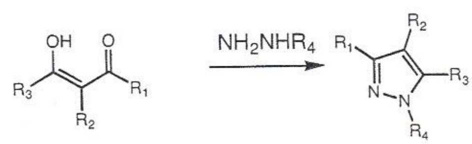
490 pages of tables containing pyrazole and benopyrazole derivatives synthesized by Eastman Kodak pre 1967

Pyrazoles, Pyrazolines, Pyrazolidine, Indazoles and Condensed Rings: Wiley
Becker Pharmaceutical database
Beilsein "inp" search function

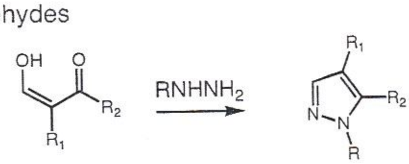
## *How to Consider and Synthesize the Pyrazole Nucleus*

- 3+2 way

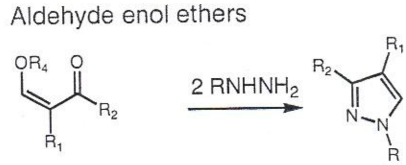




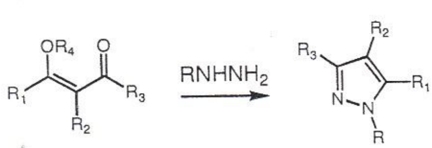
- Aldehydes



- Aldehyde enol ethers



- Ketones as enol ether... or not selective.



- Esters

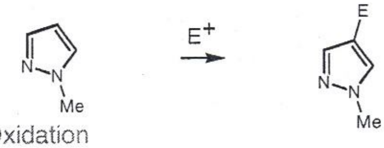
- Though dozens of other ways exist, problems of regiochemistry exist with many.

Pyrazoles, Pyrazolines, Pyrazolidine, Indazoles and Condensed Rings: Wiley

## *General Reactivity of Pyrazoles*

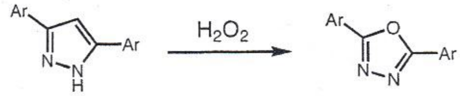
- Reaction with strong reducing agents (LAH, Stannous Chloride, Zinc dust / acetic acid, etc.) do not affect this ring system unless "special" substitution patterns.

- Electrophilic attack at $C_3$

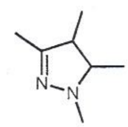



- Halogenation at $C_4$

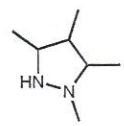

- Oxidation




- 2 references say pyrazoles are very resistent to hydrogenation, remaining unreacted with Nickel at 150°C and 100 atm $H_2$. A third says that they are readily reduced with Pd / $H_2$ at room temp to provide 2-pyrazolines, and at elevated temperatures provide pyrazolidines.

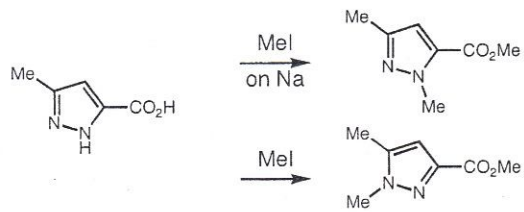


2-pyrazoline



pyrazolidine

- NH is a weak acid. Alkylation conditions can sometimes be found to selectivily alkylation.

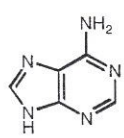



Isoxazoles part I: Grunager
Heterocyclic Chemistry: Thomas Gilchrist
Handbook of Heterocyclic Chemistry: Alan Katritzky

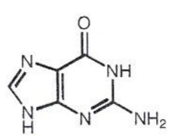
## *Imidazoles in Natural Products*

- Imidazoles are fairly common, mostly as benzoimidazoles

- DNA bases

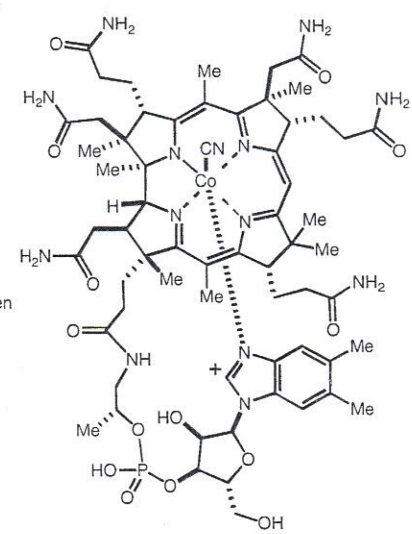


Adenine



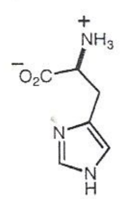
Guanine

"... I cannot help wondering whether some day a enthusiastic scientist will christen his newborn twine Adenine and Thymine." F.H. Crick

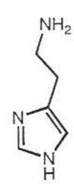


Vitamin $B_{12}$

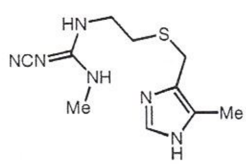
- Histidine based pharmaceuticals



Histidine



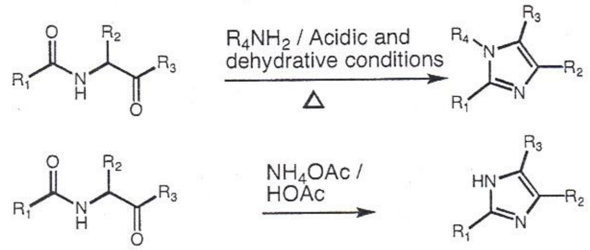
Histamine



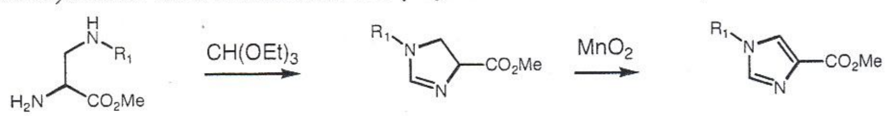
Cimetidine

## *General Approaches to Imidazoles part I*

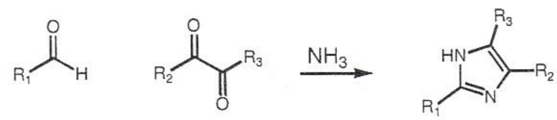
- Robinson-Gabriel / Davidson type synthesis from α-acyl aminoketones



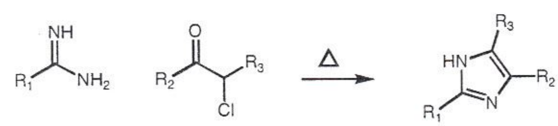

- Cyclodehydration via 2-imidazoline, many cyclization and oxidation protocols are available




- From 1-2 dicarbonyls




- From α-halo ketones

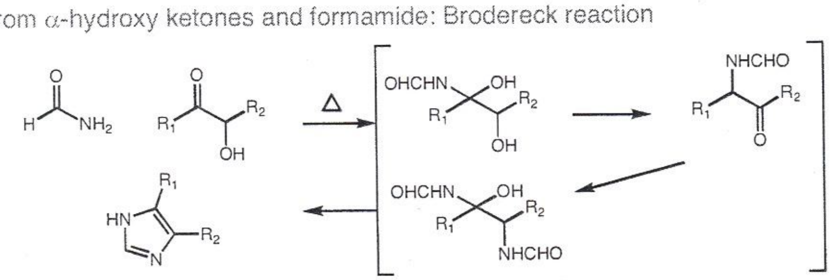




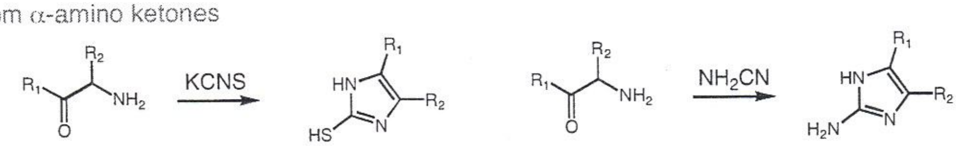
Heterocyclic Chemistry: Thomas Gilchrist
Handbook of Heterocyclic Chemistry: Alan Katritzky
ACS Short Course on Heterocyclic Chemistry
Imidazoles: Hofmann


## *General Approaches to Imidazoles part II*

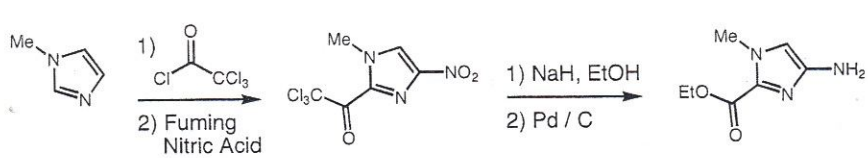
- From α-hydroxy ketones and formamide: Brodereck reaction




- From α-amino ketones




- Dervan group synthesizes imidazoles via....



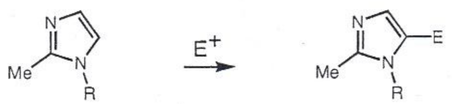


Heterocyclic Chemistry: Thomas Gilchrist
Handbook of Heterocyclic Chemistry: Alan Katritzky
ACS Short Course on Heterocyclic Chemistry
Imidazoles: Hofmann
Eric Fechter

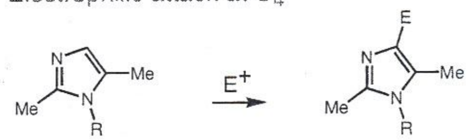
## *General Reactivity of Imidazoles*

- Imidazoles survive most oxidation conditions. The exception is when being photooxidized. They also are relatively resilient to most reductive conditions.

- Electrophilic attack at $C_5$

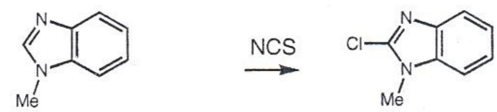



- Electrophilic attack at $C_4$

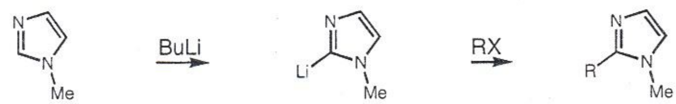



- Halogenation at N


- Halogenation at $C_2$




- Lithiation at $C_2$

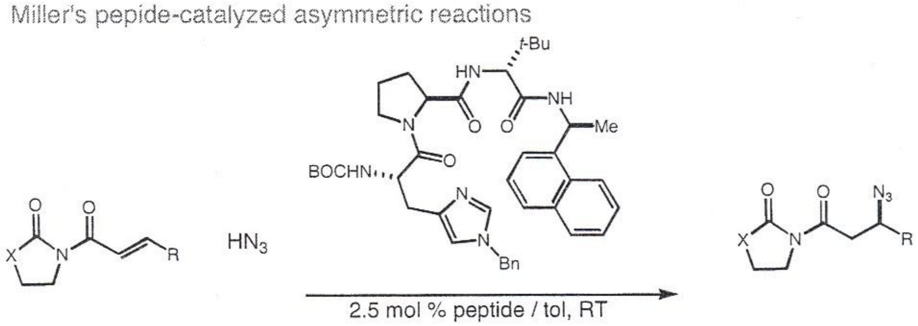




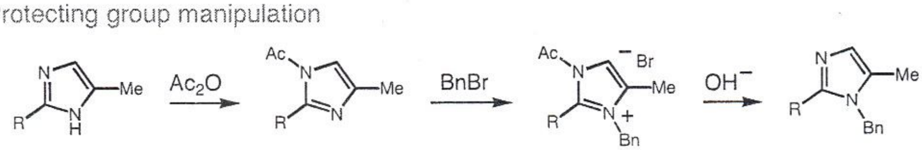
Heterocyclic Chemistry: Thomas Gilchrist
Handbook of Heterocyclic Chemistry: Alan Katritzky
ACS Short Course on Heterocyclic Chemistry
Imidazoles: Hofmann


## *Fun with Imidazoles*

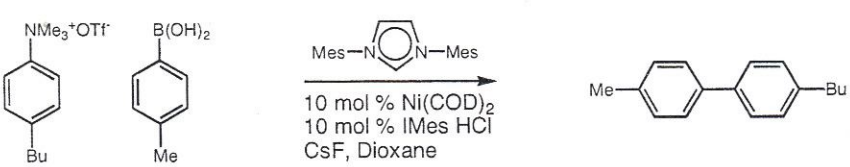
- Miller's pepide-catalyzed asymmetric reactions




- Protecting group manipulation

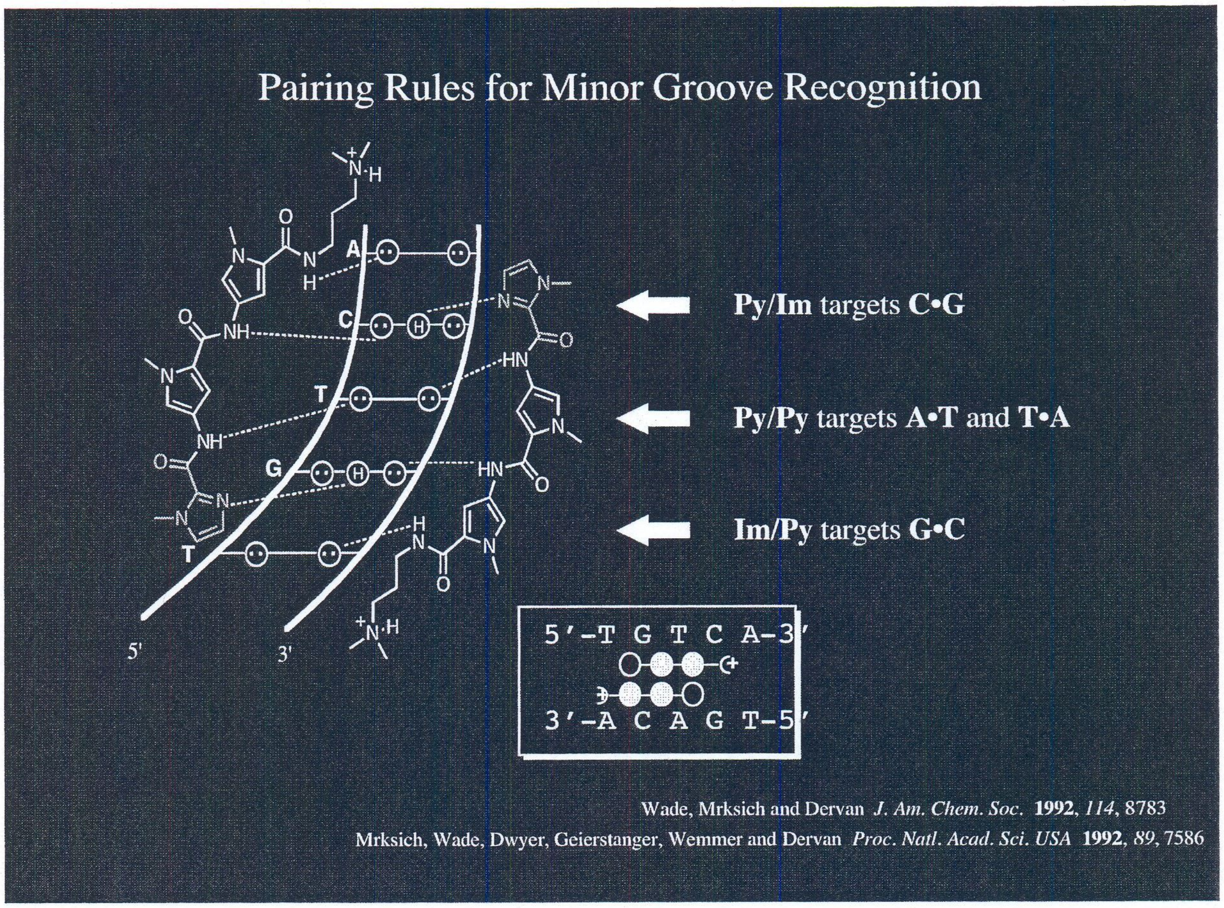



- Ligands... such as in a Simon style Suzuki





Heterocyclic Chemistry: Thomas Gilchrist
Brian Kwan Review of OC



Pairing Rules for Minor Groove Recognition
Py/Im targets C•G
Py/Py targets A•T and T•A
Im/Py targets G•C
5′-T G T C A-3′
3′-A C A G T-5′
5'
3'
Wade, Mrksich and Dervan J. Am. Chem. Soc. 1992, 114, 8783
Mrksich, Wade, Dwyer, Geierstanger, Wemmer and Dervan Proc. Natl. Acad. Sci. USA 1992, 89, 7586