

**Disclaimer:**

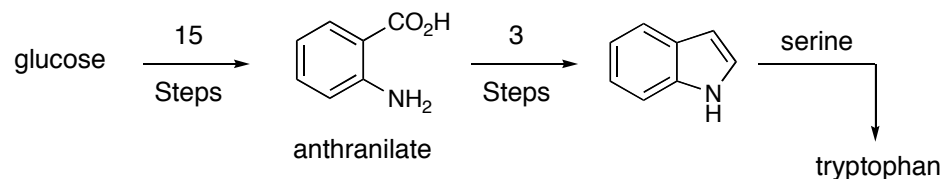
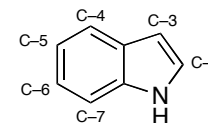
This lecture will only cover methodology for the construction of the indole and pyrrole ring systems, rather than functionalization of pre-existing heterocycles, which would be the topic of another series of lectures.

**Partial List of Transforms Discussed:**

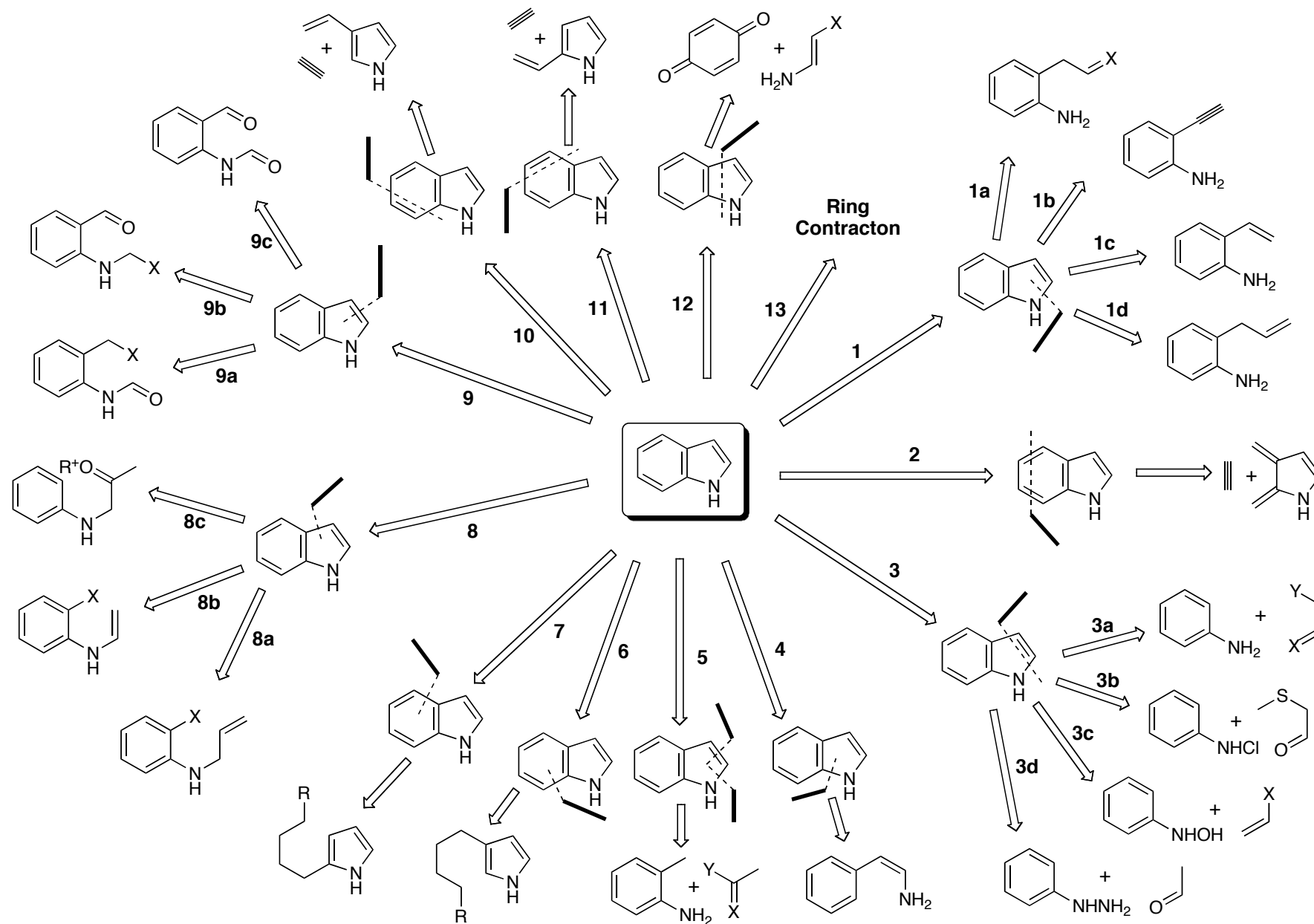
1. Batcho-Leimgruber Indole Synthesis
2. Reissert Indole Synthesis
3. Hegedus Indole Synthesis
4. Fukuyama Indole Synthesis
5. Sugasawa Indole Synthesis
6. Bischler Indole Synthesis
7. Gassman Indole Synthesis
8. Fischer Indole Synthesis
9. Japp-Klingemann Indole Synthesis
10. Buchwald Indole Synthesis
11. Bucherer Carbazole Synthesis
12. Japp-Maitland Carbazole Synthesis
13. Larock Indole Synthesis
14. Bartoli Indole Synthesis
15. Castro Indole Synthesis
16. Hemetsberger Indole Synthesis
17. Mori-Ban Indole Synthesis
18. Graebe-Ullmann Carbazole Synthesis
19. Madelung Indole Synthesis
20. Nenitzescu Indole Synthesis
21. Piloty Pyrrole Synthesis
22. Barton-Zard Pyrrole Synthesis
23. Huisgen Pyrrole Synthesis
24. Trofimov Pyrrole Synthesis
25. Knorr Pyrrole Synthesis
26. Hantzsch Pyrrole Synthesis
27. Paal-Knorr Pyrrole Synthesis
28. Zav'Yalov Pyrrole Synthesis
29. Wolff Rearrangement

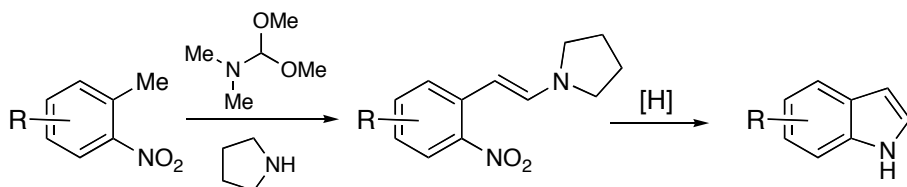
**Indole:****Nature:**

- The most abundant heterocycle in nature
- Found in tryptophan, indole-3-acetic acid (plant growth hormone), serotonin (neurotransmitter), natural products, drugs
- Isolated industrially from coal tar
- Biosynthesis of tryptophan

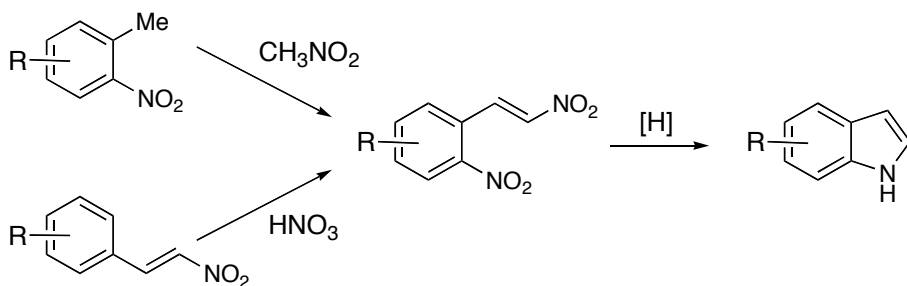
**Reactivity:**

- Isoelectronic with naphthalene (slightly lower stabilization energy)
- Indole has a higher stabilization energy than benzene
- Very weakly basic:  $\text{pK}_a$  of protonated indole:  $-2.4$
- Protonation occurs at C-3 preferentially
- Easily oxidized (atmospheric oxygen) – very electron rich
- Less prone to oxidation of EWG's on the ring – less electron rich
- Electrophilic attack occurs at C-3 (site of most electron density)
- C-3 is  $10^{13}$  times more reactive to electrophilic attack than benzene
- C-2 is the second most reactive site on the molecule, but most easily functionalized by directed lithiation
- $\text{pK}_a$  of N-H is 16.7 (20.9 DMSO)
- N-1 is the most nucleophilic site on indole
- Nucleophilic substitution at benzylic carbons enhanced
- Regiospecific functionalization of the carbocycle is difficult without pre-functionalization of the ring (i.e. halogenation)

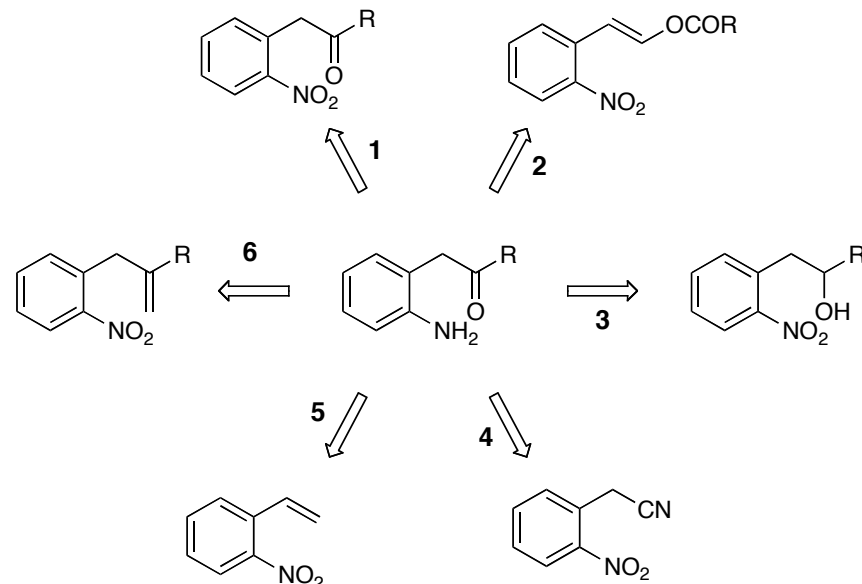


**Disconnection 1a:****Batcho-Leimgruber Indole Synthesis:**

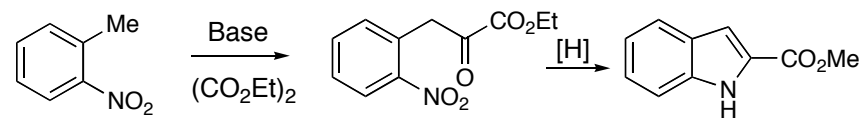
- Typical [H] = H<sub>2</sub>, Pd/C; hydrazine, Raney Ni
- Other side products from reductive cyclization include N-O
- Yields: 50's - 90's

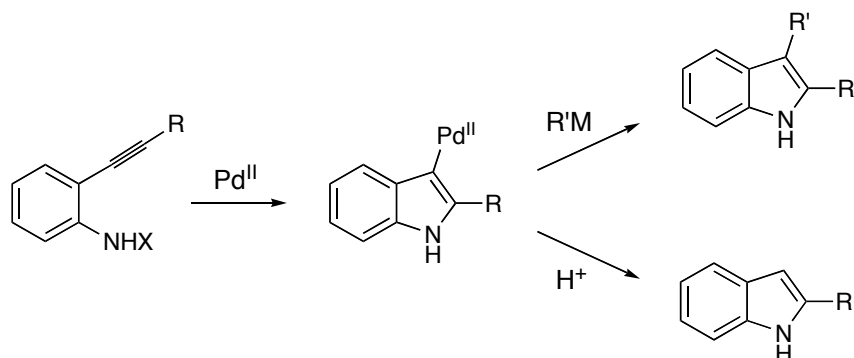
**Variants:**

- If R = carbonyl, use KF / 18-c-6 / *i*-PrOH for the Henry reaction
- Use classic Henry conditions otherwise
- Typical [H] = Fe, Fe/SiO<sub>2</sub>
- Yields: 40's - 90's

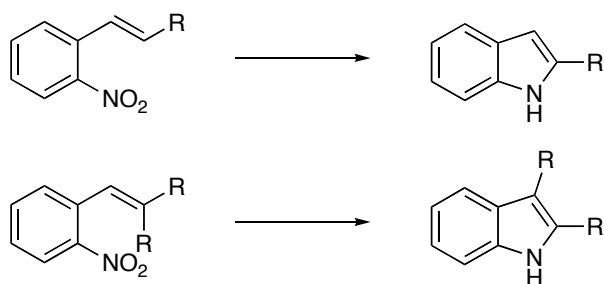
**Disconnection 1a:**

- 1: Reduction, then acid
- 2: Reduction, then acid
- 3: Oxidation, then reduction, then acid  
Can oxidize the alcohol and not the aniline with Ru(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>  
Can convert the nitro-alcohol into indole with Pd/C or Rh/C and Ru(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>
- 4: Reduction of nitro and cyano (one or two steps), then acid
- 5: Wacker oxidation, reduction, then acid
- 6: Ozonolysis, reduction, then acid

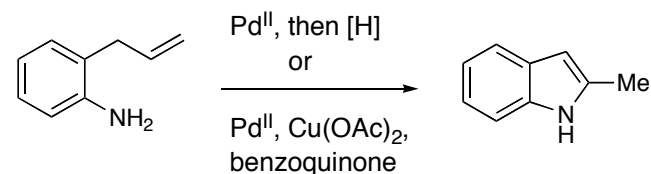
**Reissert Indole Synthesis:**

**Disconnection 1b:****Palladium Synthesis:**

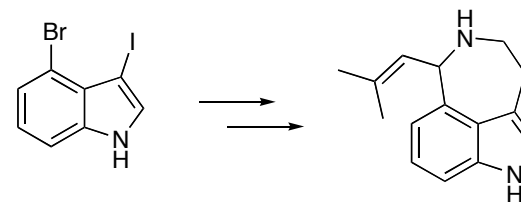
- X can be either H, Ac, Ms, TFA
- The intermediate organopalladium can be intercepted
- Yields: 40's - 90's

**Disconnection 1c:**

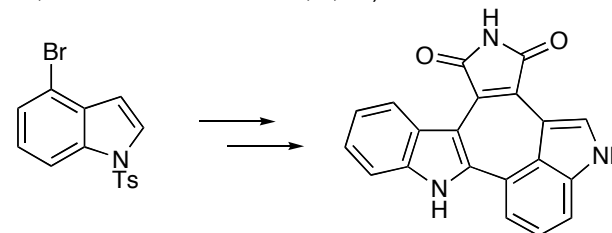
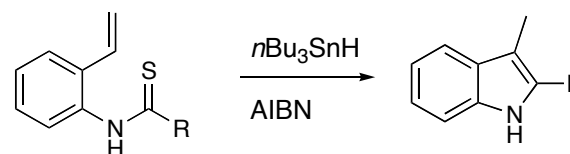
- Reductive cyclization mediated by  $(\text{EtO})_3\text{P}$  or  $\text{PdCl}_2/\text{PPh}_3/\text{SnCl}_2$  and CO
- Migratory aptitudes unknown
- Unknown mechanism - does not involve a nitrene

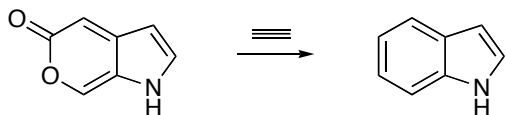
**Disconnection 1d:****Hegedus Indole Synthesis:**

- Applied to the total synthesis of *rac*-aurantioclavine by Hegedus (Hegedus, L.S. *J. Org. Chem.* **1987**, 52, 3319)

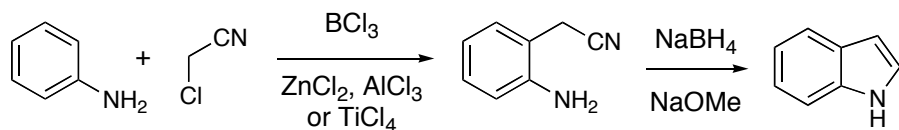


- Applied to the total synthesis of arcyriacyanin A by Steglich (Steglich, W. *Chem. Eur. J.* **1997**, 3, 70)

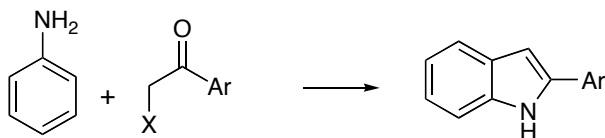
**Disconnection 1-Misc.:****Fukuyama Indole Synthesis:**

**Disconnection 2:****Pyrrone Diels-Alder:**

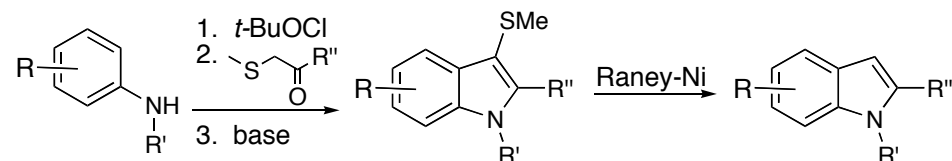
- Little regiocontrol observed in most reactions
- pyrrole-quinodimethanes are not stable and therefore not amenable for Diels-Alders directly

**Disconnection 3a:****Sugasawa Indole Synthesis:**

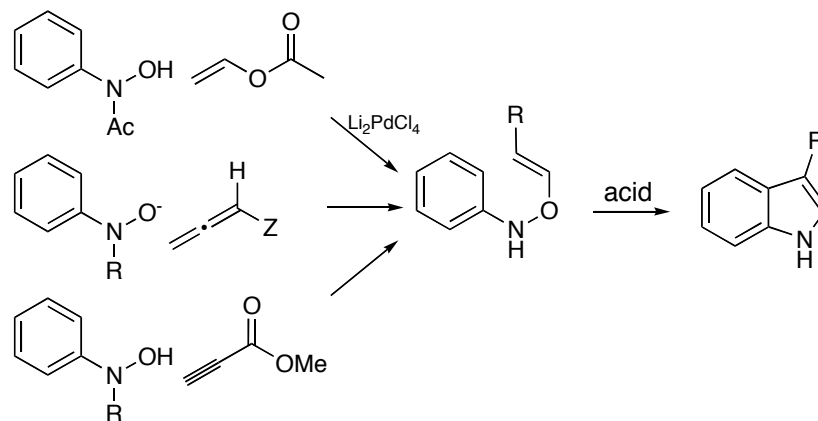
- Requires very strong Lewis Acids so many functionalities are not stable
- Choice of second Lewis acid depends on substitution pattern

**Bischler Indole Synthesis:**

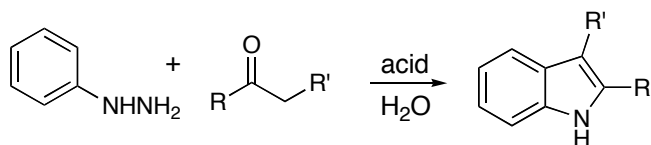
- Not very general: requires HBr (1 eq) and 200+ °C
- **Mechanism?**

**Disconnection 3b:****Gassman Indole Synthesis:**

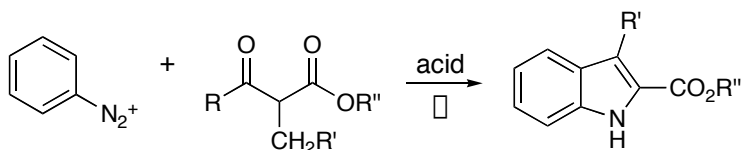
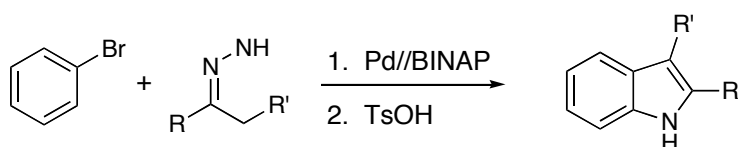
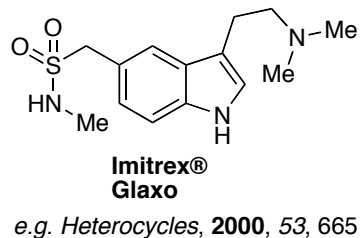
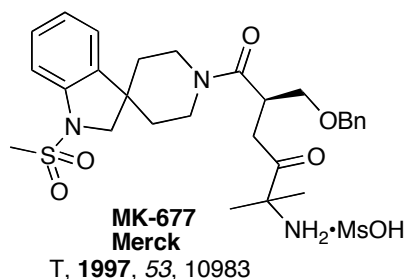
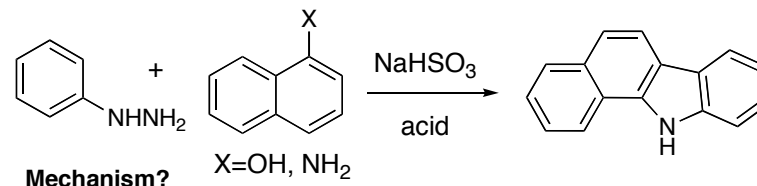
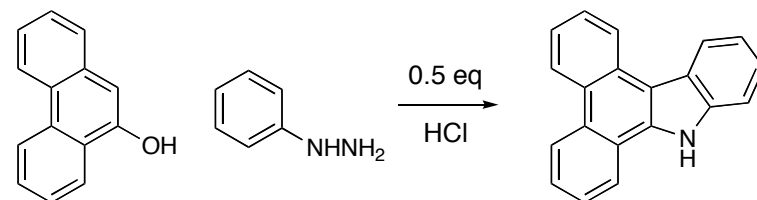
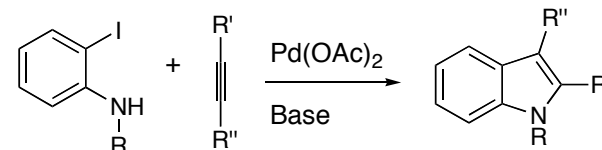
- Good regiocontrol observed with ortho or para substitution
- ortho/para methoxy substituents failed completely

**Disconnection 3c:**

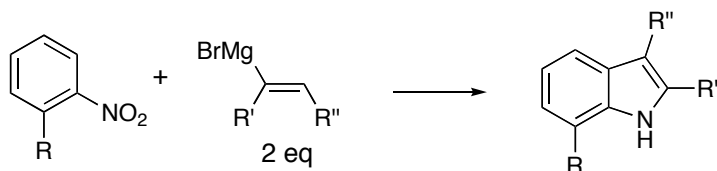
- Quite mild, if the O-vinyl derivatives can be synthesized

**Disconnection 3d:****Fischer Indole Synthesis:**

- Common acids: HCl, H<sub>2</sub>SO<sub>4</sub>, PPA, BF<sub>3</sub>/AcOH, ZnCl<sub>2</sub>, FeCl<sub>3</sub>, AlCl<sub>3</sub>, CoCl<sub>2</sub>, NiCl<sub>2</sub>, TsOH
- Regioselectivity not great with unsymmetrical ketones
- Tolerates a wide range of substitution
- Product regioselectivity affected by choice of acid, solvent, temperature

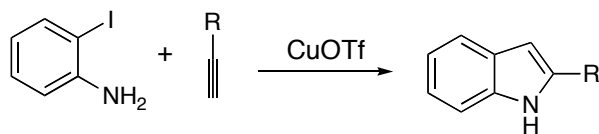
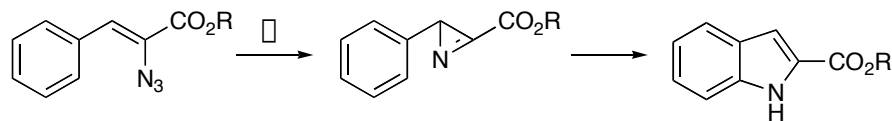
**Japp-Klingemann Modification:****Buchwald Modification:****Pharmaceutical Applications of the Fischer Indole Synthesis:****Disconnection 3d:****Bucherer Carbazole Synthesis:****Japp-Maitland Condensation:****Disconnection 3-Misc.:****Larock Indole Synthesis:**(Larock, R.C. *J. Org. Chem.* 1998, 63, 7652)

- Base additives vary by reaction
- High functional group tolerance
- Bulkier R group placed at C-2 of the indole

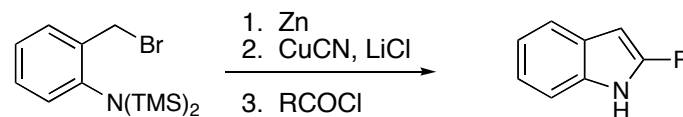
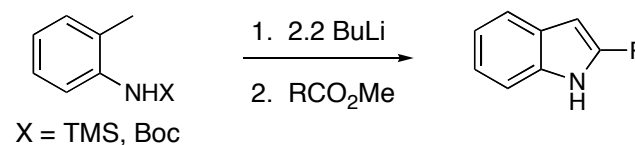
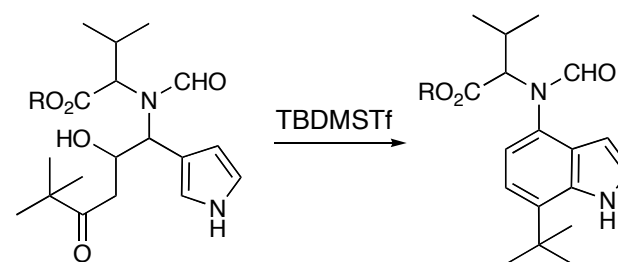
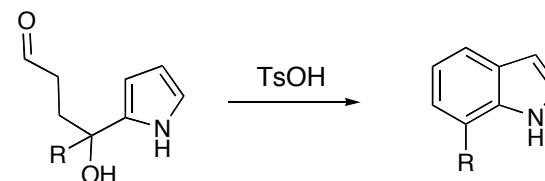
**Disconnection 3–Misc.:****Bartoli Indole Synthesis:**

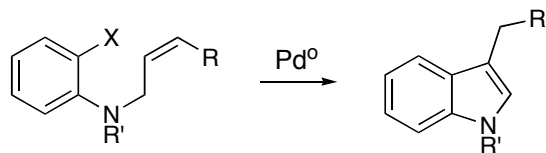
– Mechanism?

– Only works well with 2-substituted nitrobenzenes

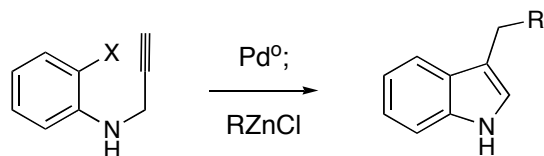
**Castro Indole Synthesis:****Disconnection 4:****Hemetsberger Indole Synthesis:**

- Formed by condensation of aromatic aldehyde with  $\alpha$ -azooester with NaOEt, under very carefully controlled conditions to prevent N<sub>2</sub> loss
- Yields = 30's – 90's
- Unknown mechanism – not a nitrene insertion reaction

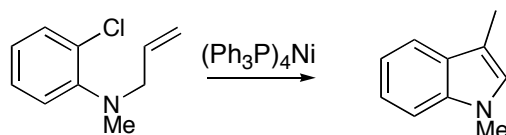
**Disconnection 5:****Stepwise:****One pot:****Disconnection 6:****Disconnection 7:**

**Disconnection 8a:****Heck Approach:**

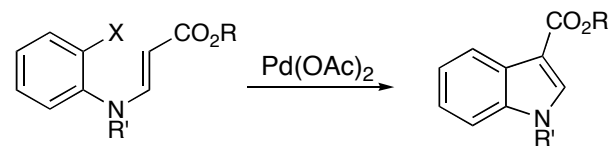
- Yields = 70's - 90's
- Choice of base and protecting group on the nitrogen can affect the yield

**More Palladium:**

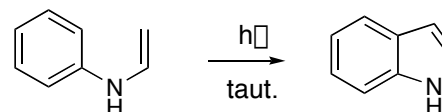
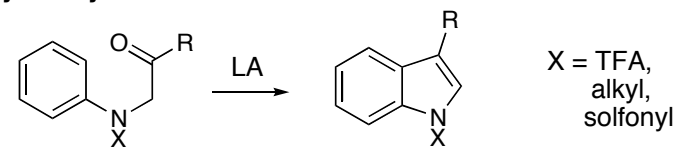
- Can intercept the intermediate organopalladium species
- Any organozinc reagent can be used to transmetallate.

**Mori-Ban Indole Synthesis:**

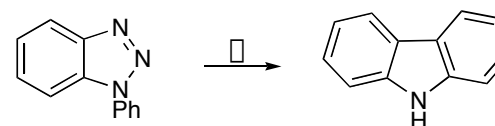
- Requires stoichiometric nickel
- Yields only about 50%.

**Disconnection 8b:****More Palladium:**

- Works best with an EWG on the olefin

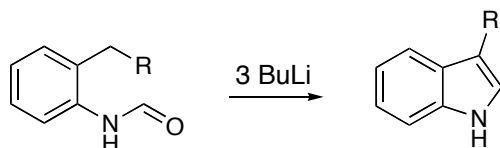
**Photochemical:****Disconnection 8c:****Acid Catalyzed Cyclization:**

- LA commonly  $ZnCl_2$
- Can also use ketals with  $BF_3$  or  $TiCl_4$

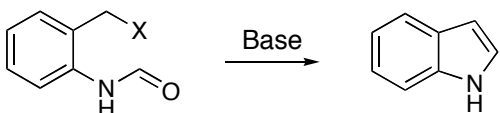
**Disconnection 8-Misc.:****Graebe-Ullmann Carbazole Synthesis:**

- **Mechanism?**
- Generally problematic and not widely applicable

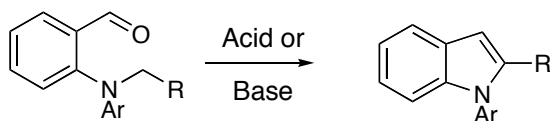
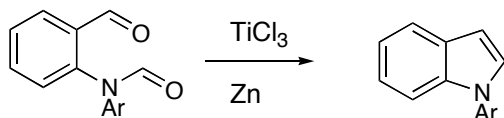
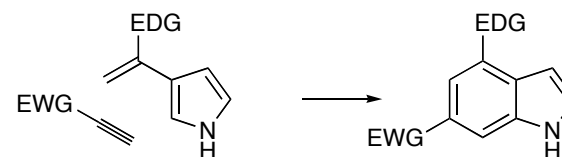


**Disconnection 9a:****Madelung Synthesis:**

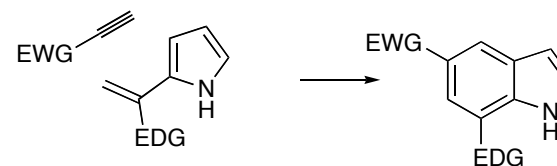
– Yields = 40's – 90's

**Variant of Madelung:**

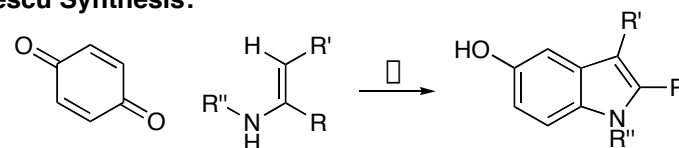
- Where X is a phosphorous, nitrogen, silicon, or oxygen to stabilize a negative charge
- If X is phosphorous, then it is an intramolecular Wittig.

**Disconnection 9b:****Base/Acid Catalyzed closure:****Disconnection 9c:****McMurray Type Closures:****Disconnection 10:****Diels-Alder:**

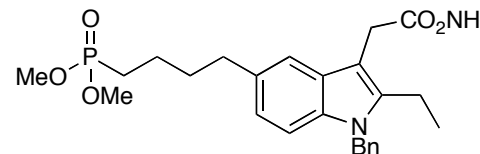
– Works best when matched

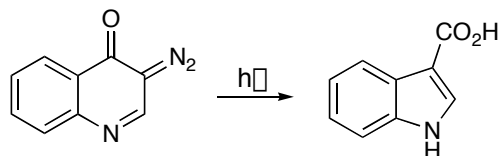
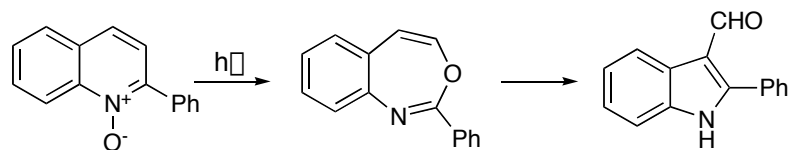
**Disconnection 11:****Diels-Alder:**

– Works best when matched

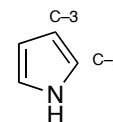
**Disconnection 12:****Nenitzescu Synthesis:**

- **Mechanism?**
- Substitution on the quinone ring is acceptable and predictable
- Substitution on the enamine is tolerated, but R' is best as an EWG
- Used in the synthesis of LY311727 (Lilly)

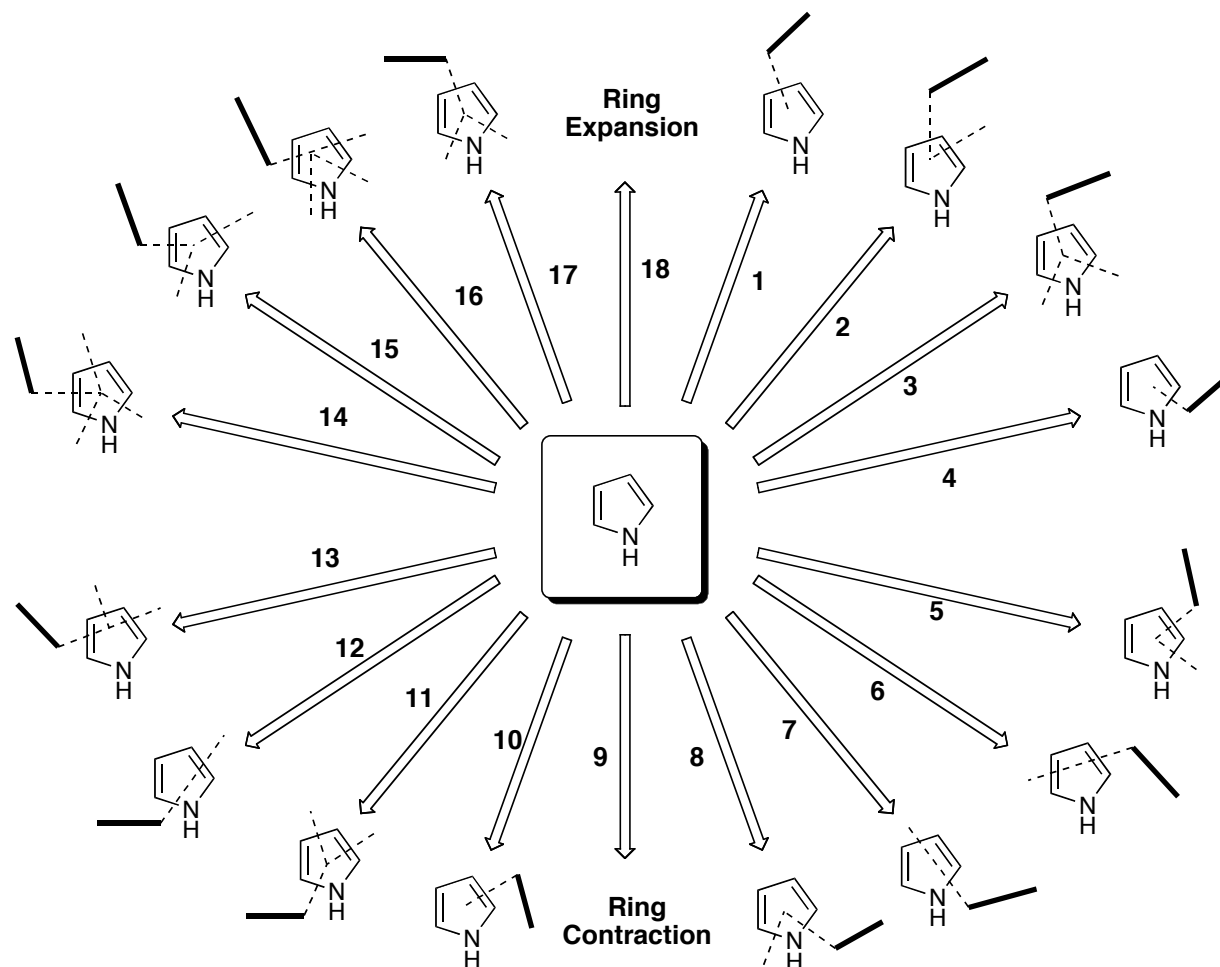


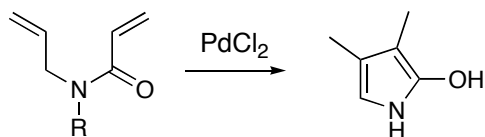
**Disconnection 13:****Wolff Rearrangement:****From Quinolines:****Pyrrole:****Nature:**

- Very abundant in nature
- Found in porphyrins, natural products, drugs
- Isolated industrially from coal tar and/or bone oil

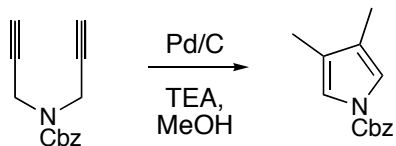
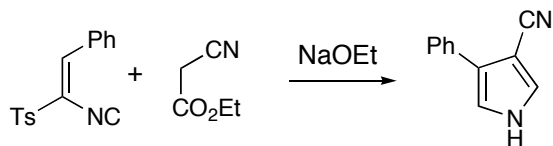
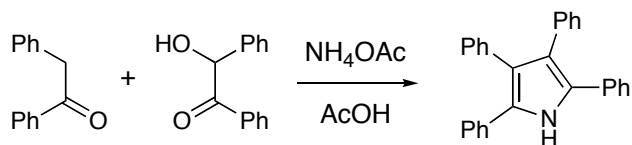
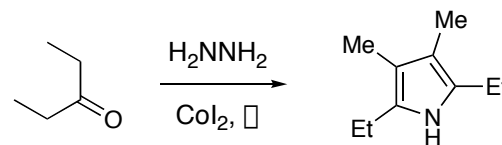
**Reactivity:**

- Protonation occurs at C-2 preferentially
- Easily oxidized (atmospheric oxygen) – very electron rich
- Quickly colorizes upon exposure to air
- Less prone to oxidation of EWG's on the ring – less electron rich
- Decomposition and polymerization rapid with acid
- Electrophilic attack occurs at C-2 (site of most electron density)
- C-3 is the second most reactive site on the molecule
- pK<sub>a</sub> of N-H is 23 (DMSO)
- N-1 is the most nucleophilic site on pyrrole

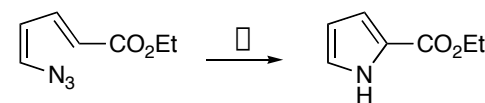
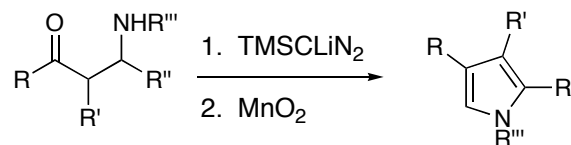
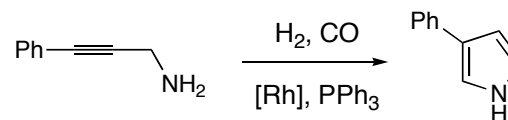


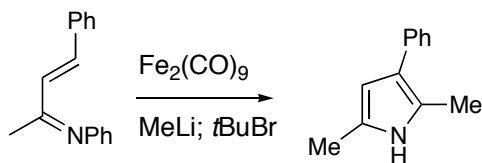
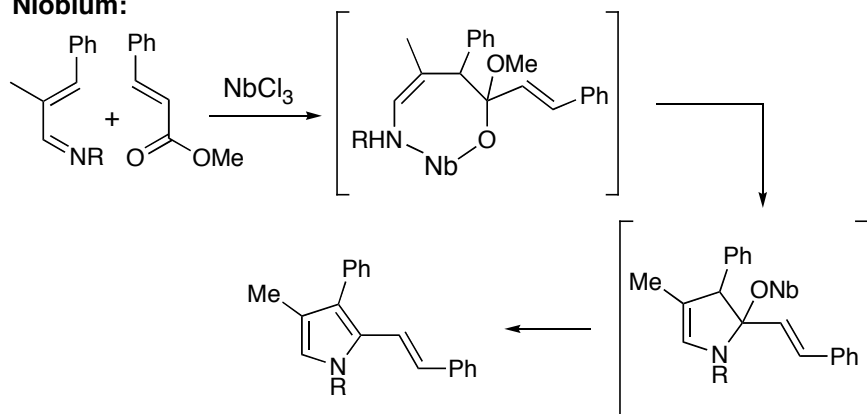
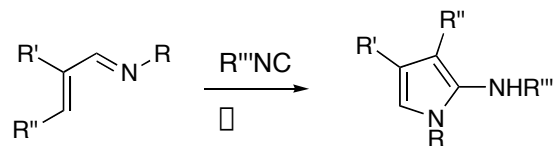
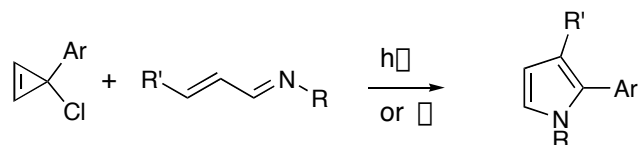
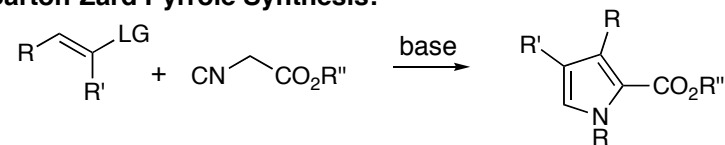
**Disconnection 1:****Palladium with Alkenes:**

– Exists mainly in the tautomeric form

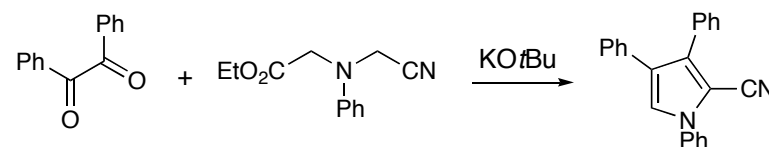
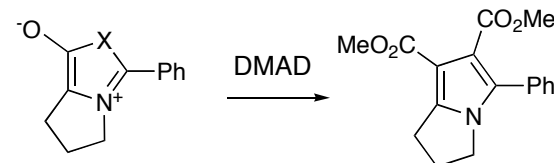
**Palladium with Alkynes:****Disconnection 2:****Disconnection 3:****Disconnection 3:****Piloty Synthesis:**

– Mechanism?

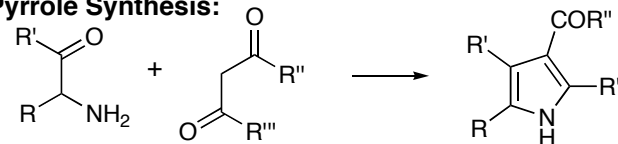
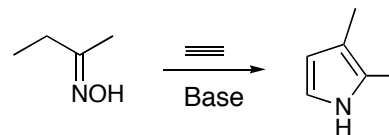
**Disconnection 4:****Thermal Cyclization:****Carbene Insertion:****Disconnection 5:****Rhodium:**

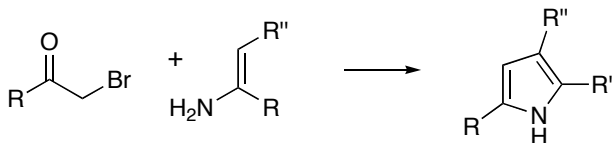
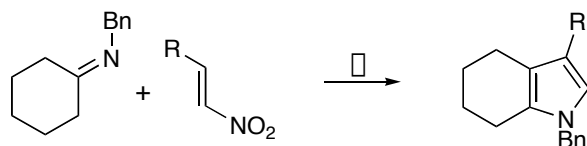
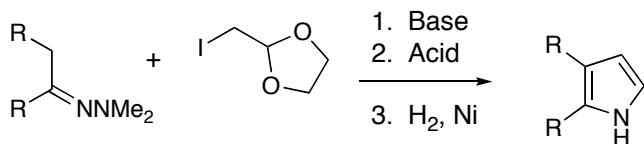
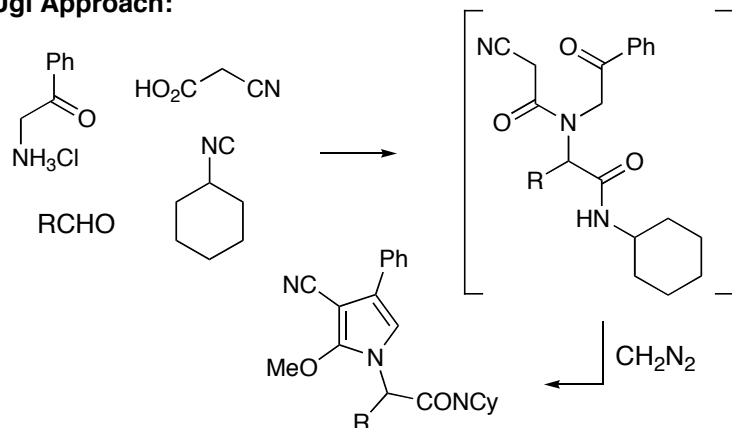
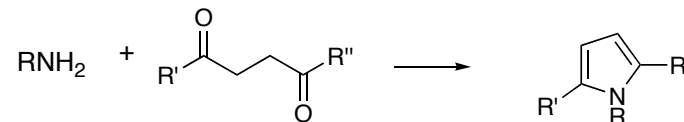
**Disconnection 5 Continued:****Iron:****Niobium:****2-Aminopyrroles:****From Cyclopropenes:****Disconnection 6:****Barton-Zard Pyrrole Synthesis:**

– Original Barton-Zard used  $\text{NO}_2$  as the LG.

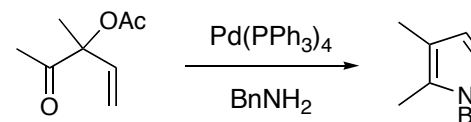
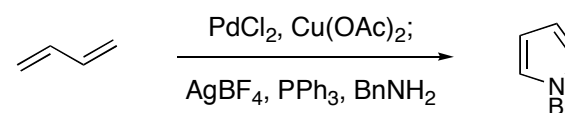
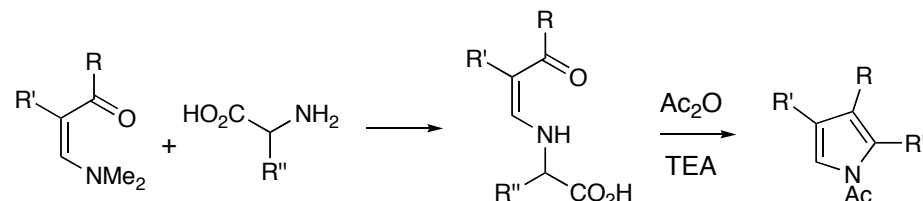
**Bis-Nucleophile/Bis-Electrophile:****Extrusion (Huisgen Pyrrole Synthesis):**

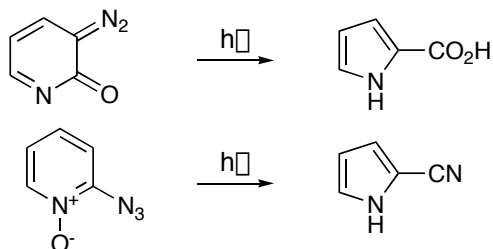
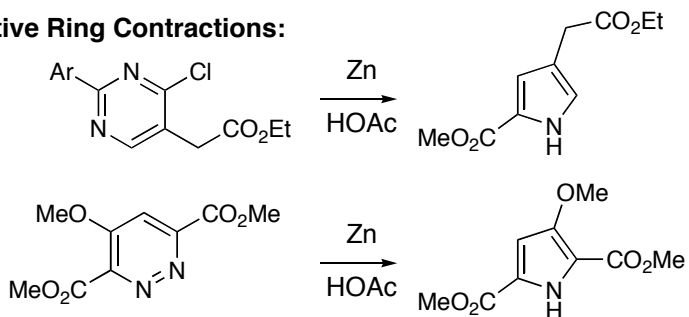
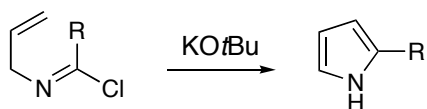
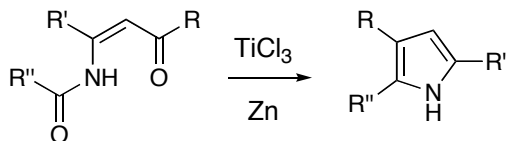
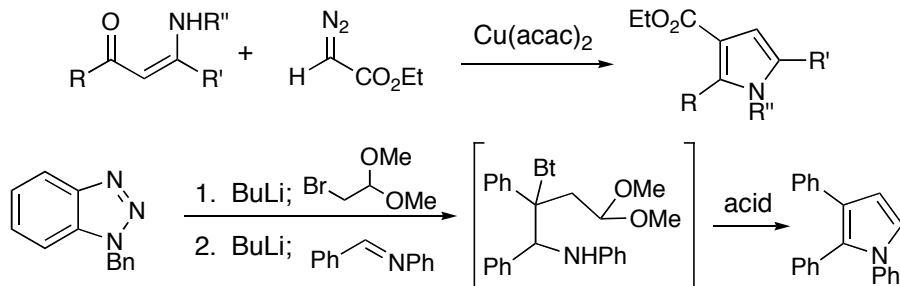
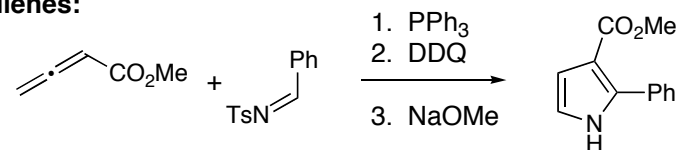
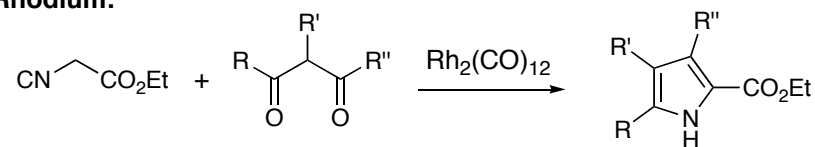
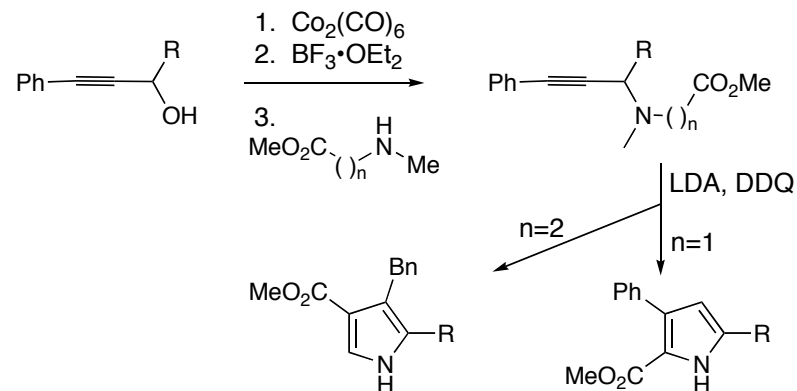
– X is usually S or NR

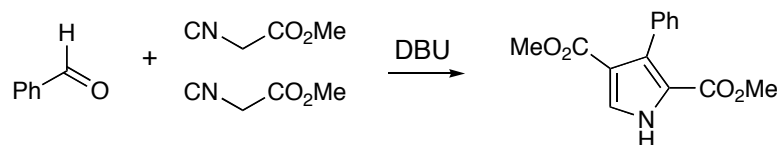
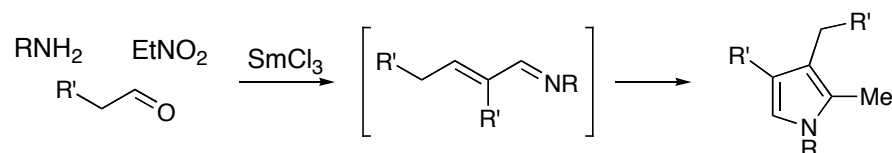
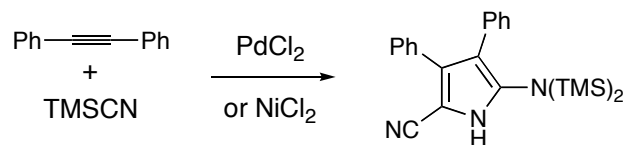
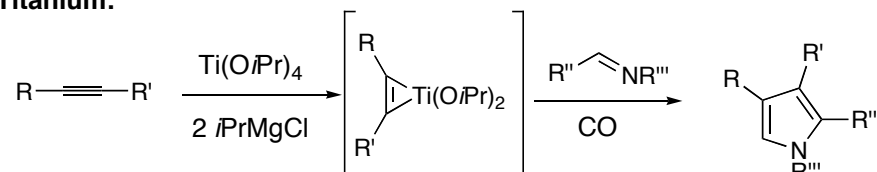
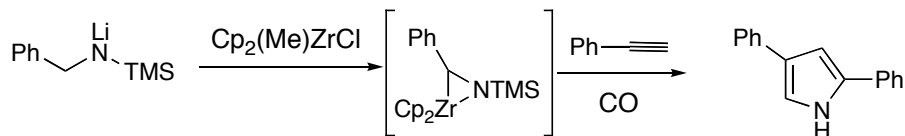
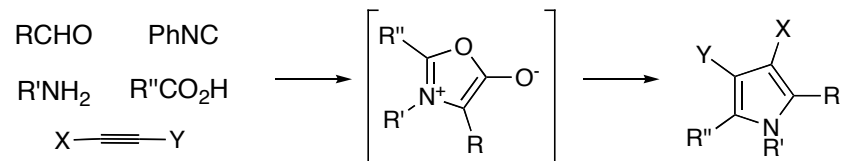
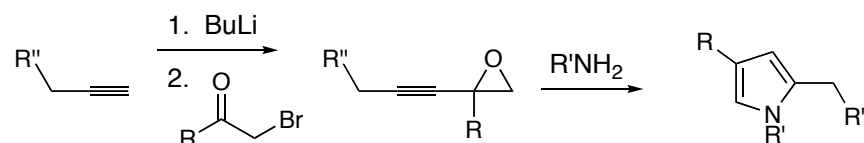
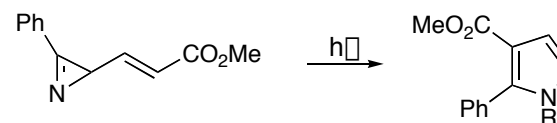
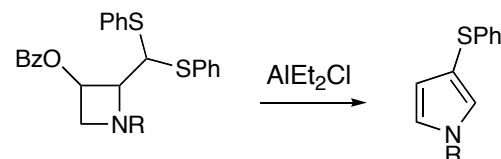
**Disconnection 7:****Knorr Pyrrole Synthesis:****Trofimov Pyrrole Synthesis:**

**Disconnection 7 Continued:****Hantzsch Pyrrole Synthesis:****Formal 3+2:****Stepwise:****Ugi Approach:****Disconnection 8:****Paal-Knorr Pyrrole Synthesis:**

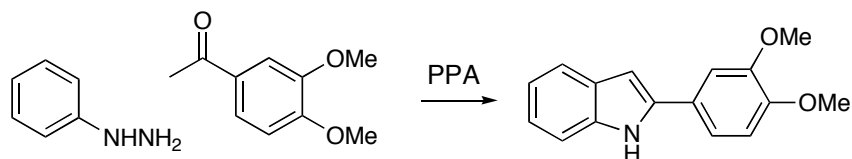
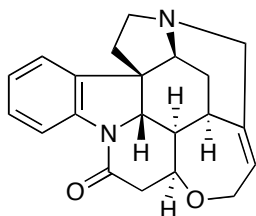
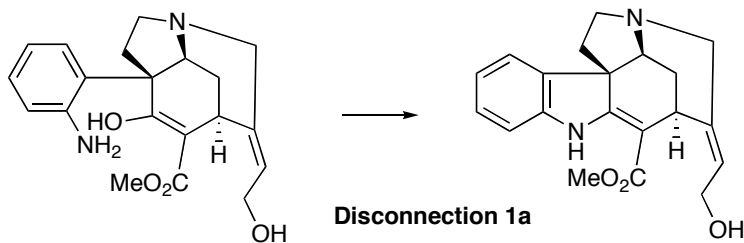
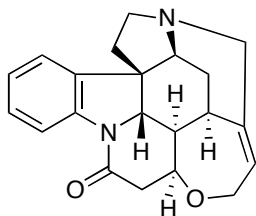
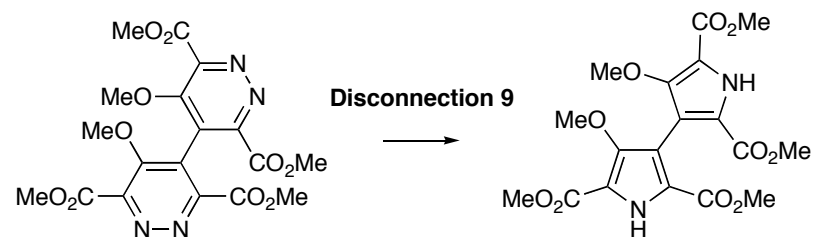
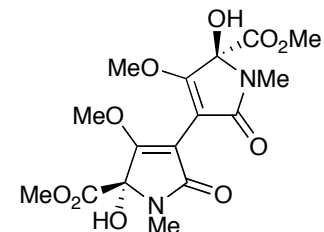
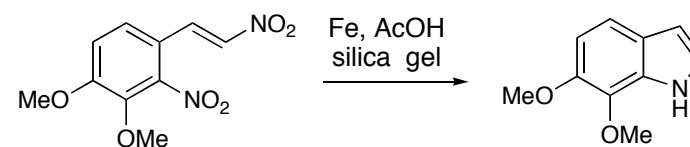
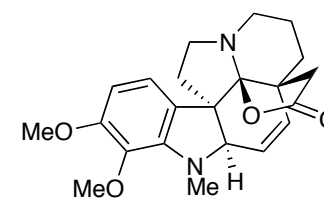
- Can access the diketone *in-situ* by reduction of the bis-cyano compound
- Can access via reduction of the  $\alpha$ -nitro ketone

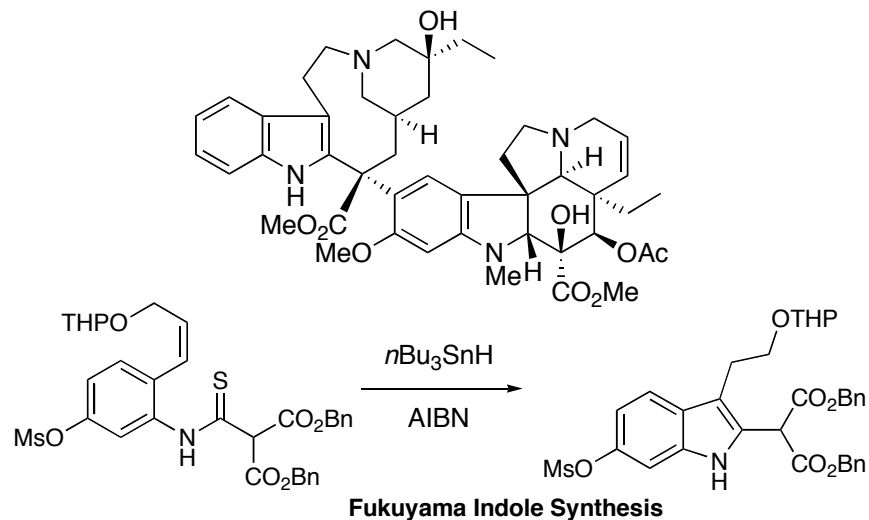
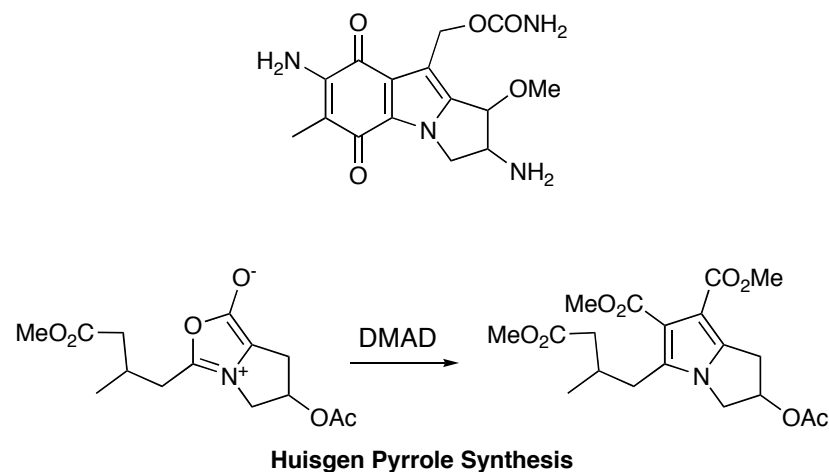
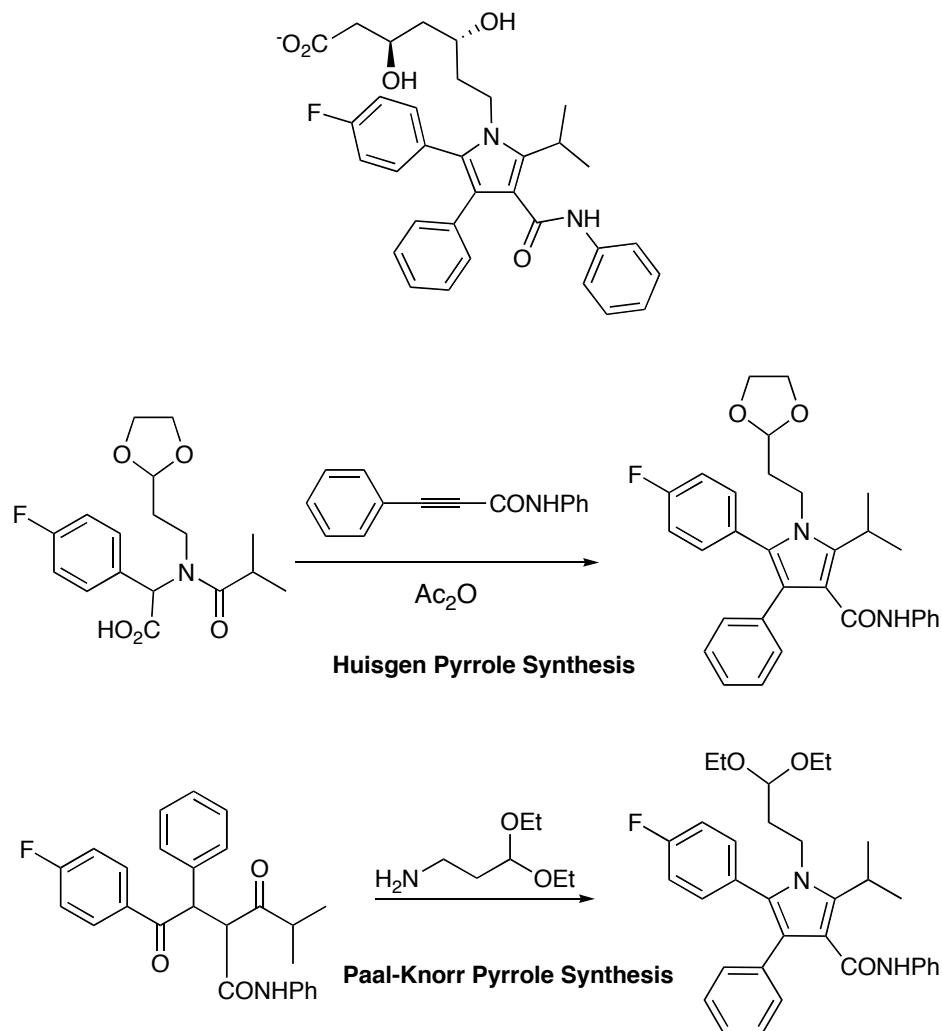
**Palladium:****Zav'Yalov Pyrrole Synthesis:**

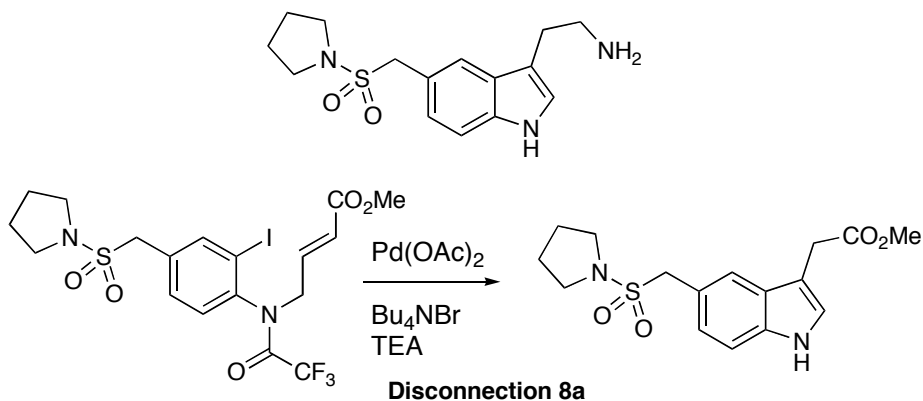
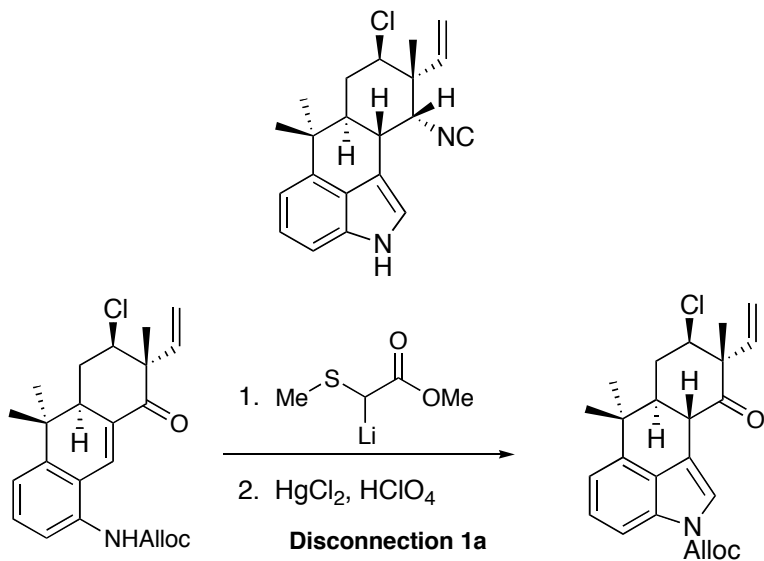
**Disconnection 9:****Wolff Rearrangement/Photolytic:****Reductive Ring Contractions:****Disconnection 10:****Base Catalyzed:****McMurray Type Coupling:****Disconnection 11:****Disconnection 12:****Allenes:****Rhodium:****Cobalt:**

**Disconnection 13:****Disconnection 14:****Disconnection 15:****Palladium:****Titanium:****Zirconium:****Disconnection 16:****Disconnection 17:****Disconnection 18:****From Cyclopropanes:****From Cyclobutanes:**

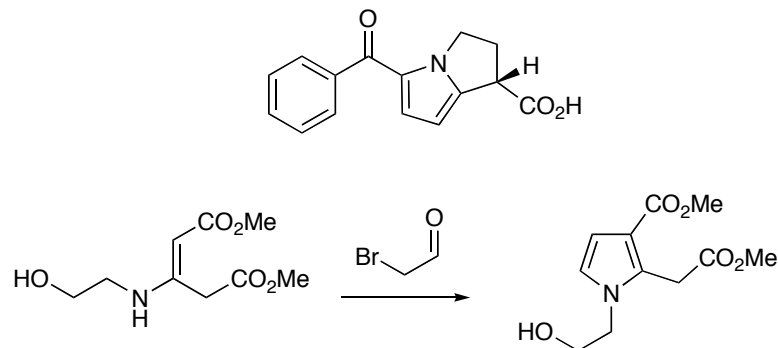
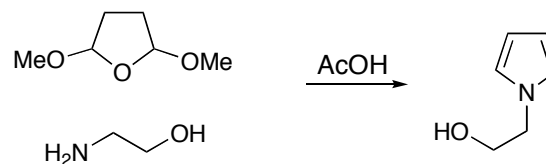


**Selected Syntheses:****Strychnine: Woodward (Classics I)****Fischer Indole Synthesis****Strychnine: Overman (Classics I)****Disconnection 1a****Selected Syntheses:****Isochrysohermidin: Boger (Classics II)****Disconnection 9****Aspidophytine: Corey (Classics II)****Batcho-Leimgruber Indole Synthesis Variant**

**Selected Syntheses:****Vinblastine: Fukuyama (Classics II)****Mitosene: Rebek (*J. Org. Chem.* 1984, 49, 5164)****Selected Syntheses:****Lipitor®: Pfizer (Li, J.J. *Contemporary Drug Synthesis.* Wiley. 2004)**

**Selected Syntheses:**Axert®: Janssen (Li, J.J. *Contemporary Drug Synthesis*. Wiley. 2004)Hapalindole G: Fukuyama (*J. Am. Chem. Soc.* 1994, 116, 3125)**Selected Syntheses:**Ketorolac®: Syntex (Muchowski, *Adv. Med. Chem.* 1992, 1, 109)

- 1<sup>st</sup> Generation strategies utilize pyrrole syntheses
- Process synthesis uses annulation starting from pyrrole

**Hantzsch Pyrrole Synthesis****Paal-Knorr Pyrrole Synthesis**