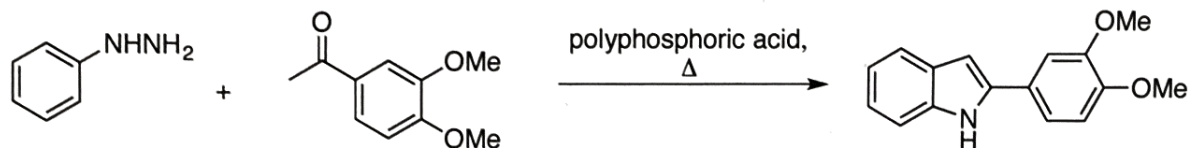


Adapted from

Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*, 1st ed.; Wiley-VCH: Weinheim, 1996.

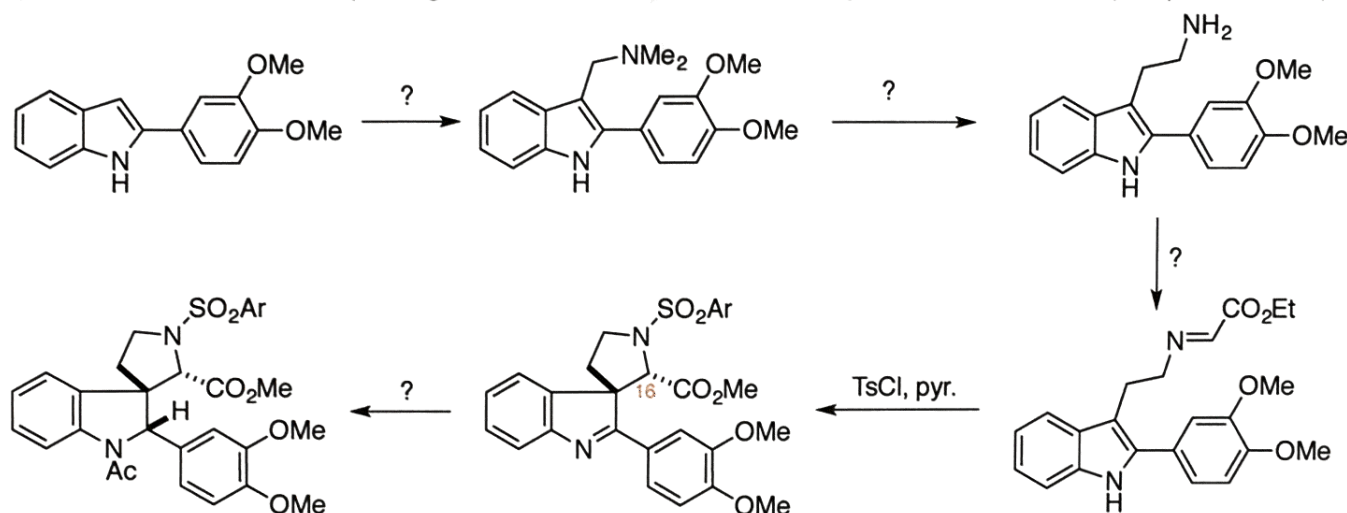
Original references: a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749; b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

1. Propose a mechanism for the following transformation of phenylhydrazine with acetoveratone.

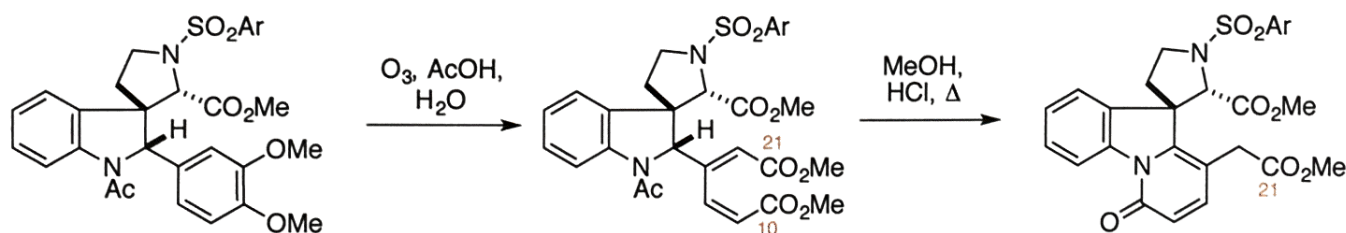


What is the name for this reaction? Sketch an energy profile diagram for all steps, clearly indicating relative energies of all intermediates. Give a simple rationale for your choices.

2. Provide reagents where there are question marks. Provide a mechanism for the reaction of the Schiff base to the spiroannulated indolenine, explaining the stereochemical outcome of only one diastereoisomer (see position C-16).



3. Suggest a mechanism for the lactamization reaction below, which includes a full chemoselective justification of the position of C-21 in the product.



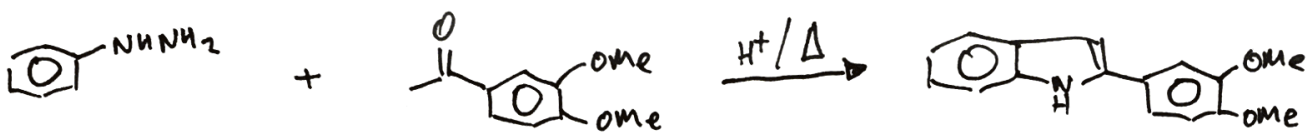
4. Woodward's clever use of acetoveratone installs a functional group with a dual role. Later in the synthesis it is unmasked by ozonolysis to reveal a diene (see scheme above). By considering your solution to question 2, explain the other role that this aromatic group plays. Make use of resonance hybrids/ mesomeric forms to illustrate your points.

The indoline is protected for only one step in the synthesis: explain. Would a Bn protecting group work?

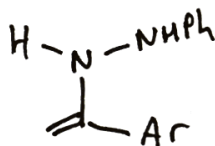
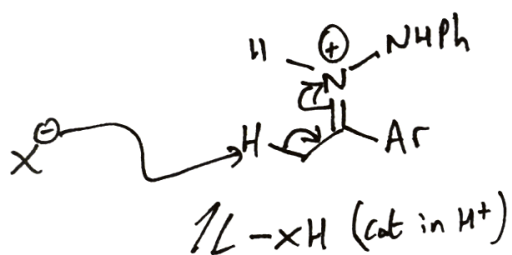
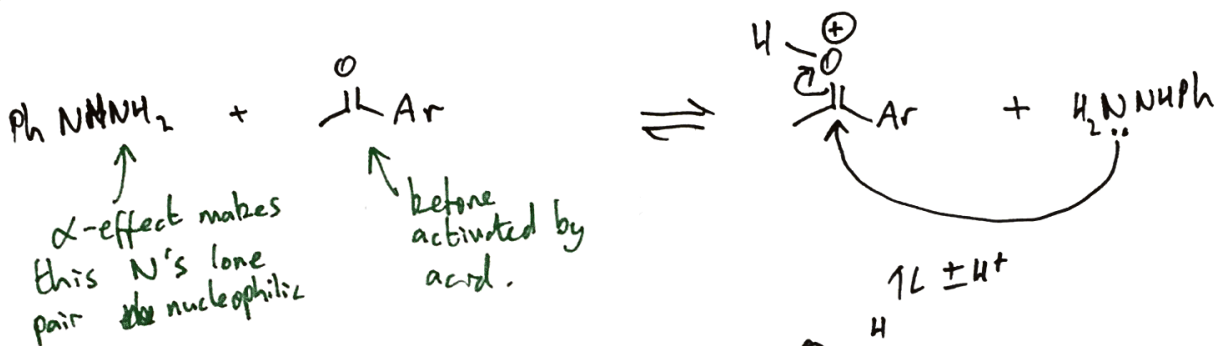
5. Time permitting: provide the ozonolysis mechanism, here without NaBH₄, or DMS or PPh₃.

① The Fisher Indole Synthesis

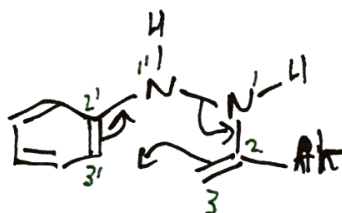
rxn of phenyl/aromatic hydrazine with a ketone or aldehyde, going through a [3,3]-sigmatropic rearrangement, to give an indole.



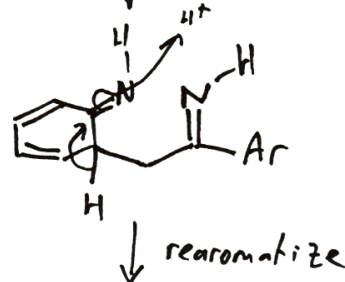
i) First step is H^+ cat. dehydration to make iminium/enamine eq^m



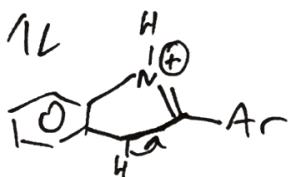
\equiv redraw in more suggestive form



[3,3]- σ , probably first irreversible step (energy profile)

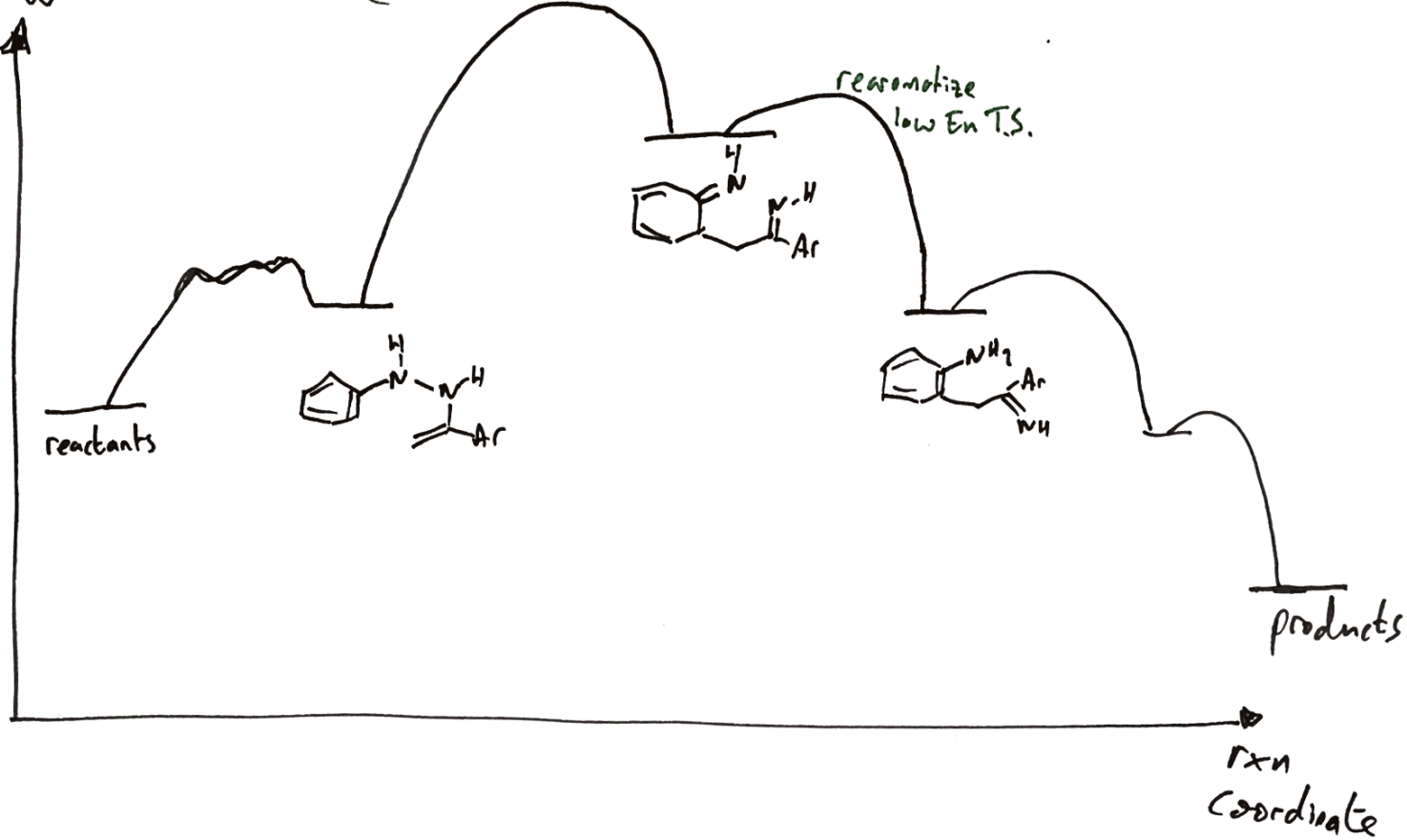


using N lone pair.

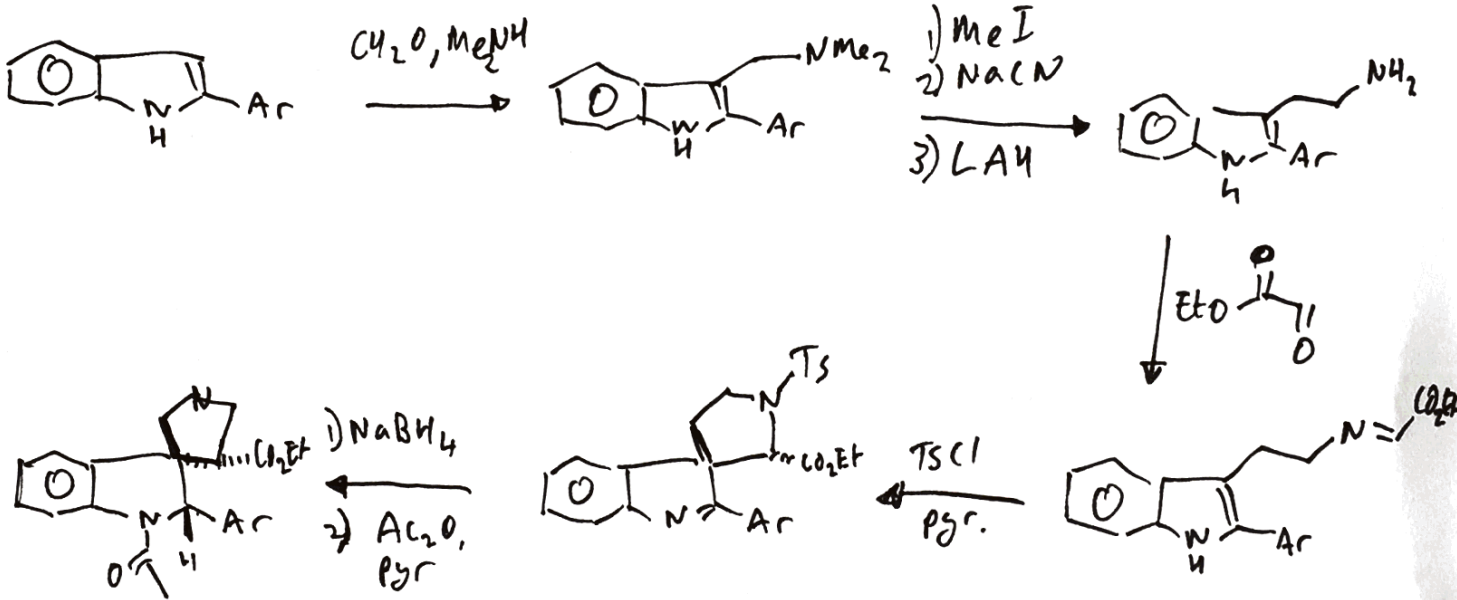


Energy

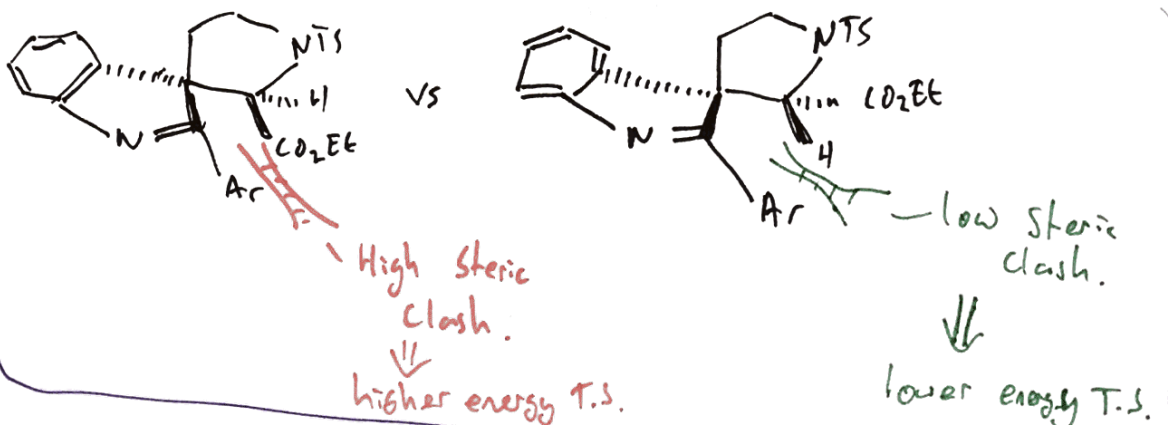
[3,3]-sigmatropic high E_a T.S.



2

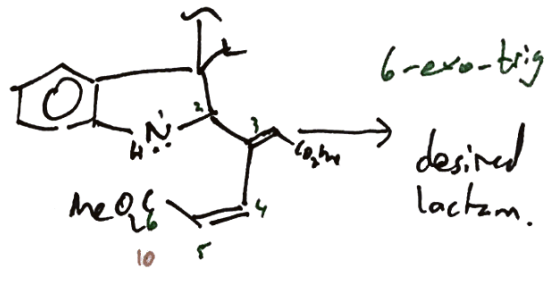
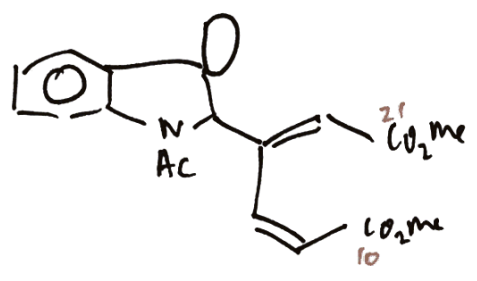


diastereoisomers.

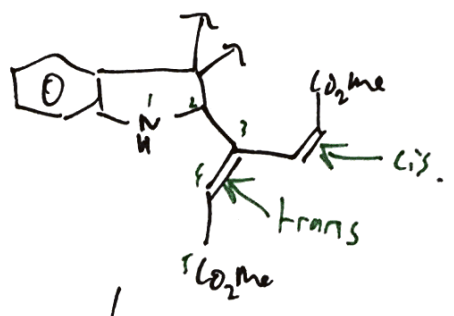


3

lactamizatⁿ



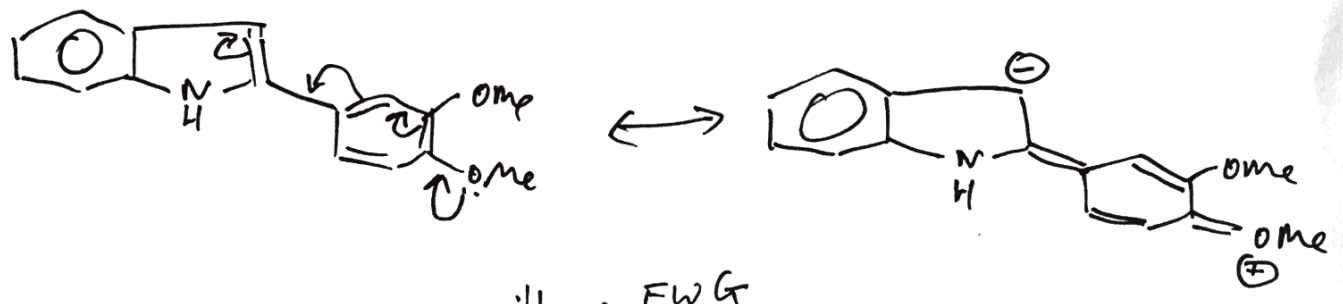
or



5-exo-trig.
normally faster
but trans alkene

X

4) Protects reactive 2-position of indole
and increases reactivity of 3-position of indole.



with an EWG

Needed to be protected (to stop amine reacting with reactive intermediates / oxidants / electrophiles in ozonolysis rxn.)

Also, improves/eliminates any chemoselectivity issues by reducing e density in indole ring.

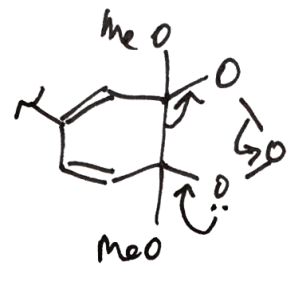
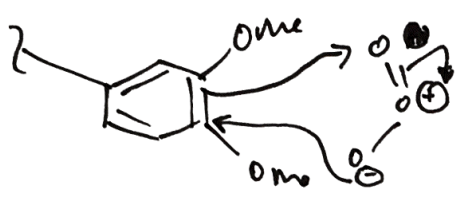
5

Regio selectivity

highly electron rich double bond.

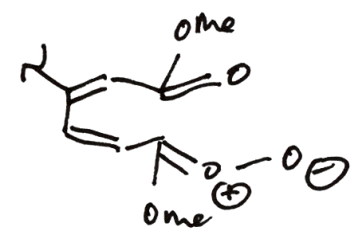


1,3-dipolar cycloaddⁿ

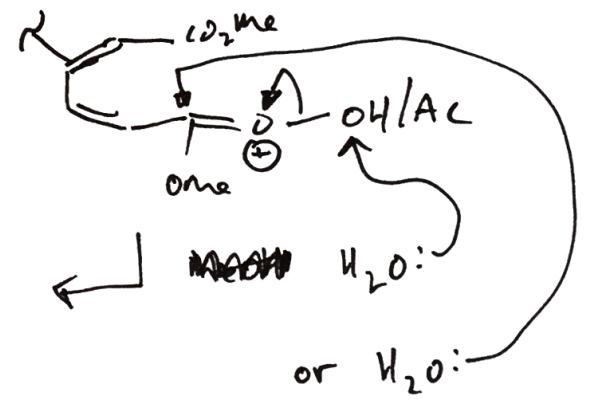


reverse 1,3-dipolar cycloaddⁿ.

Cannot rotate and make ozonide



H⁺ / ~~H₂O~~ → $\equiv\text{O}^+$



prod