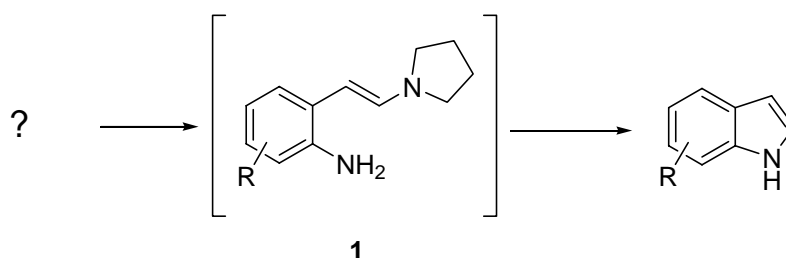


Chemistry of Indoles

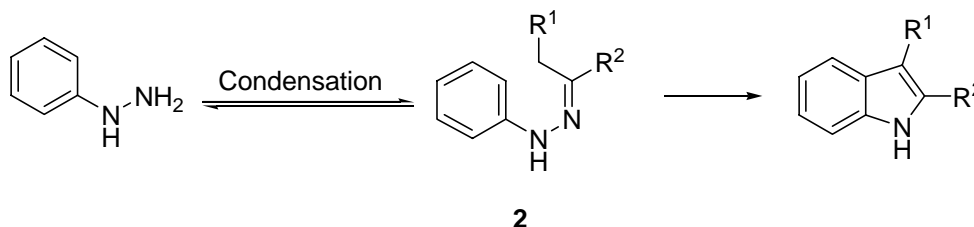
A: Synthesis of Indoles

- The Leimgruber-Batcho Synthesis of indole is often used to generate indoles with substituents on the carbocycle. Suggest a mechanism for the final stage of this reaction, which occurs spontaneously:



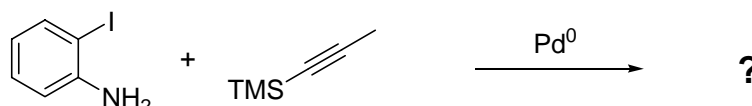
Suggest a method of synthesising **1**.

- The first synthesis of indole, discovered in 1883, was the Fischer indole synthesis. This method works well with 2- and 3- substituted indoles. Show the mechanism for this reaction:



The requirement for an aryl hydrazine starting material limits the range of substituents that can be included on the carbocycle ring. Show how a modified Buchwald amination reaction could be used to generate the phenyl hydrazone intermediate (**2**) from a simpler starting material.

- What product would you expect from the following reaction (hint: it's an indole):

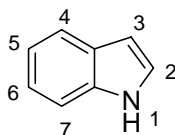


Only one regioisomer is seen in this reaction. Show how this regioselectivity originates.

B: Reactions of Indoles

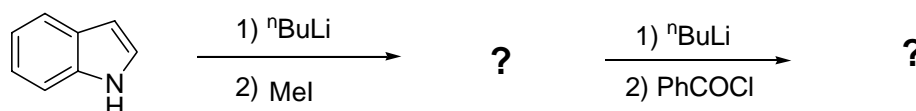
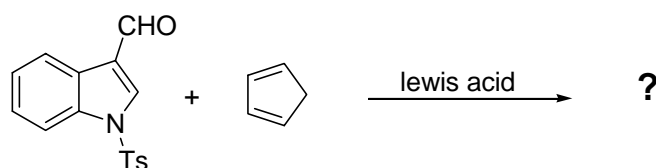
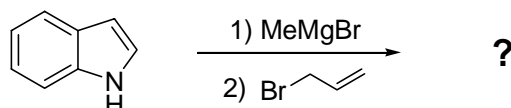
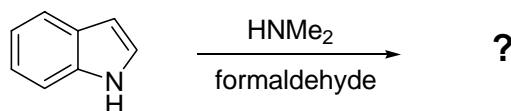
Indoles are aromatic heterocycles, but exhibit very distinctive reactivity. Here are some general rules:

- The nitrogen is **not** basic ($pK_a -3.6$)
- Indole can readily undergo aromatic electrophilic substitution. The C-3 position is the most nucleophilic, followed by the N and C-2 positions.

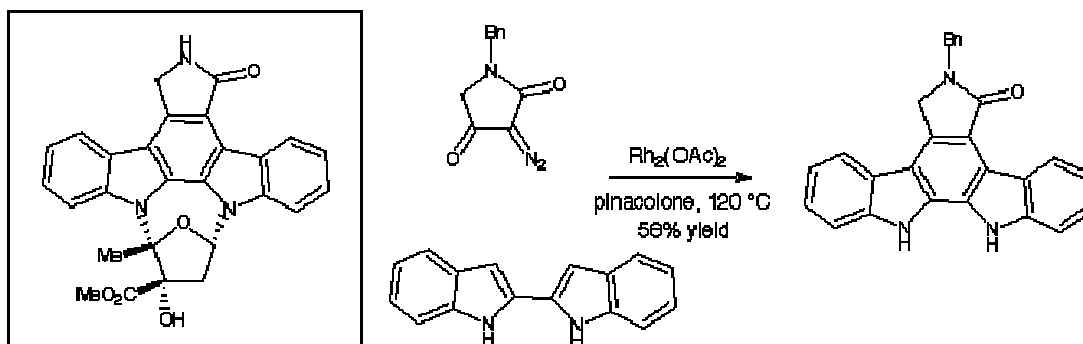


- The C-2 – C-3 bond can often react like an alkene
- Indole can be deprotonated at nitrogen ($pK_a 21$). The resulting salts can be good nucleophiles.
 - Highly ionic salts (eg. Li^+ , K^+) favour N substitution.
 - Softer counterions favour C-3 substitution.
- When N is substituted, C-2 can be deprotonated.

Predict the outcomes of these reactions:



Wood recently reported a very clever approach to the synthesis of the indolocarbazole family of natural products (*JACS* 1995, 117, 10413). His approach to the indolocarbazole core is the one-pot transformation outlined below.



Provide a plausible mechanism for this multi-step transformation in the space below.