Chemistry of Indoles

A: Synthesis of Indoles

1. 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:

   \[ \text{?} \rightarrow \begin{array}{c} \text{R} \text{NH}_2 \\ \text{R} \end{array} \rightarrow \text{R} \text{N} \text{H} \]

   1

   Suggest a method of synthesising 1.

2. 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:

   \[ \text{Condensation} \rightarrow \begin{array}{c} \text{R}^1 \\ \text{R}^2 \end{array} \rightarrow \text{R}^1 \text{N} \text{H} \text{R}^2 \]

   2

   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 hydrazine intermediate (2) from a simpler starting material.

3. What product would you expect from the following reaction (hint: it’s an indole):

   \[ \text{I} \text{NH}_2 + \text{TMS} \text{Pd}^0 \rightarrow ? \]

   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.

\[
\begin{align*}
\text{N} & \quad \text{H} \\
1 & \quad 2 \\
3 & \quad 4 \\
5 & \quad 6 \\
7 & \quad 8
\end{align*}
\]

- 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 (e.g. 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:

1. \[
\begin{align*}
\text{Indole} & \quad \text{HNMe}_2 \\
\text{formaldehyde} & \quad \text{?}
\end{align*}
\]

2. \[
\begin{align*}
\text{Indole} & \quad 1) \text{MeMgBr} \\
\text{Br} & \quad 2) \text{CH}_2=\text{CH}_2 \\
\text{?}
\end{align*}
\]

3. \[
\begin{align*}
\text{Indole} & \quad \text{Ts} \\
\text{CHO} & \quad \text{Cyclopentadiene} \\
\text{lewis acid} & \quad \text{?}
\end{align*}
\]

4. \[
\begin{align*}
\text{Indole} & \quad 1) \text{^6BuLi} \\
\text{2) Mel} & \quad \text{?} \\
\text{?} & \quad 1) \text{^6BuLi} \\
\text{2) PhCOCl} & \quad \text{?}
\end{align*}
\]
Wood recently reported a very clever approach to the synthesis of the indocarbazole family of natural products (JACS 1998, 120, 10613). His approach to the indocarbazole core is the one-pot transformation outlined below.

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