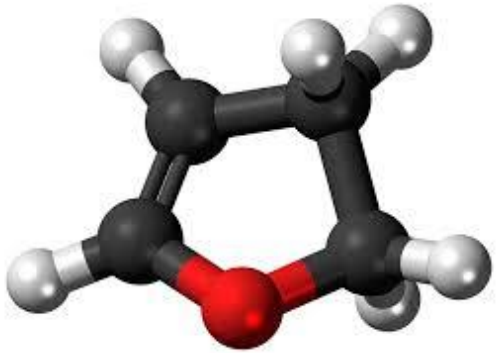
2302687 – Heterocyclic Compounds – Part I

Lecture 2-5

Heteroaromatic Synthesis via Metal Catalysis



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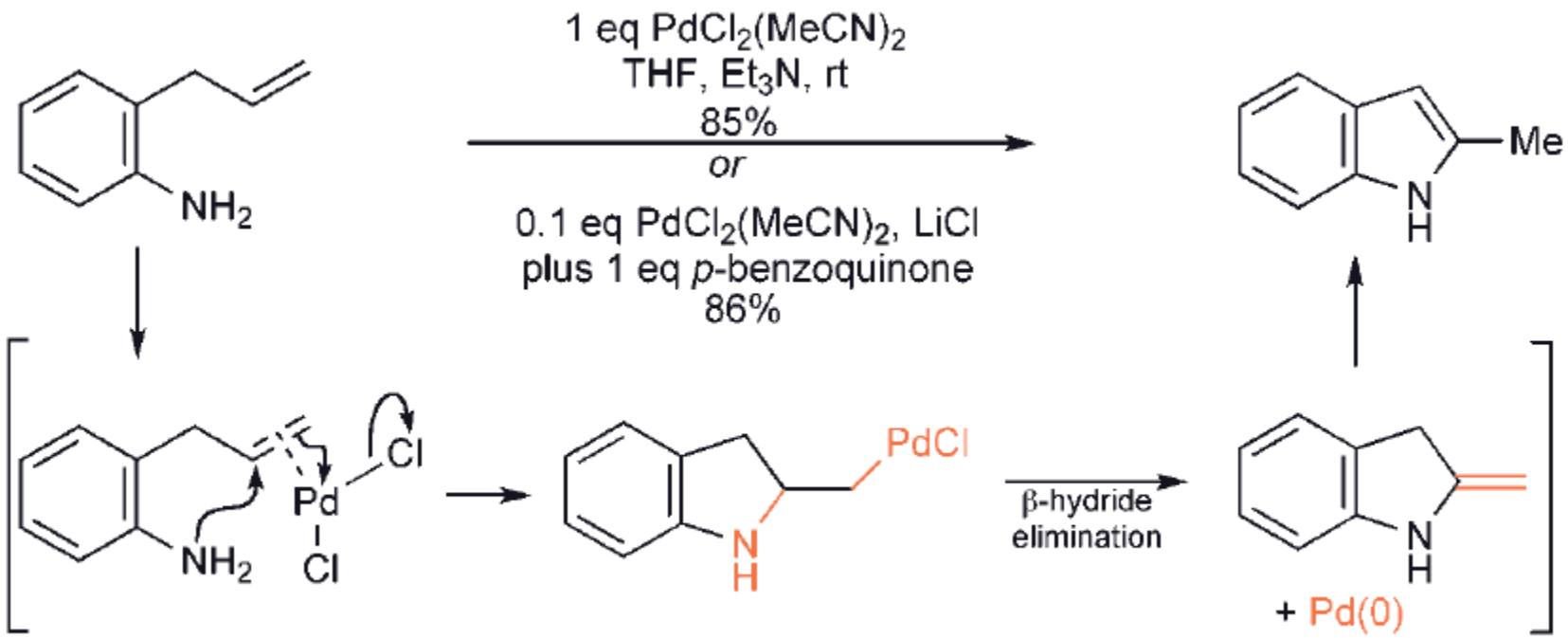
Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

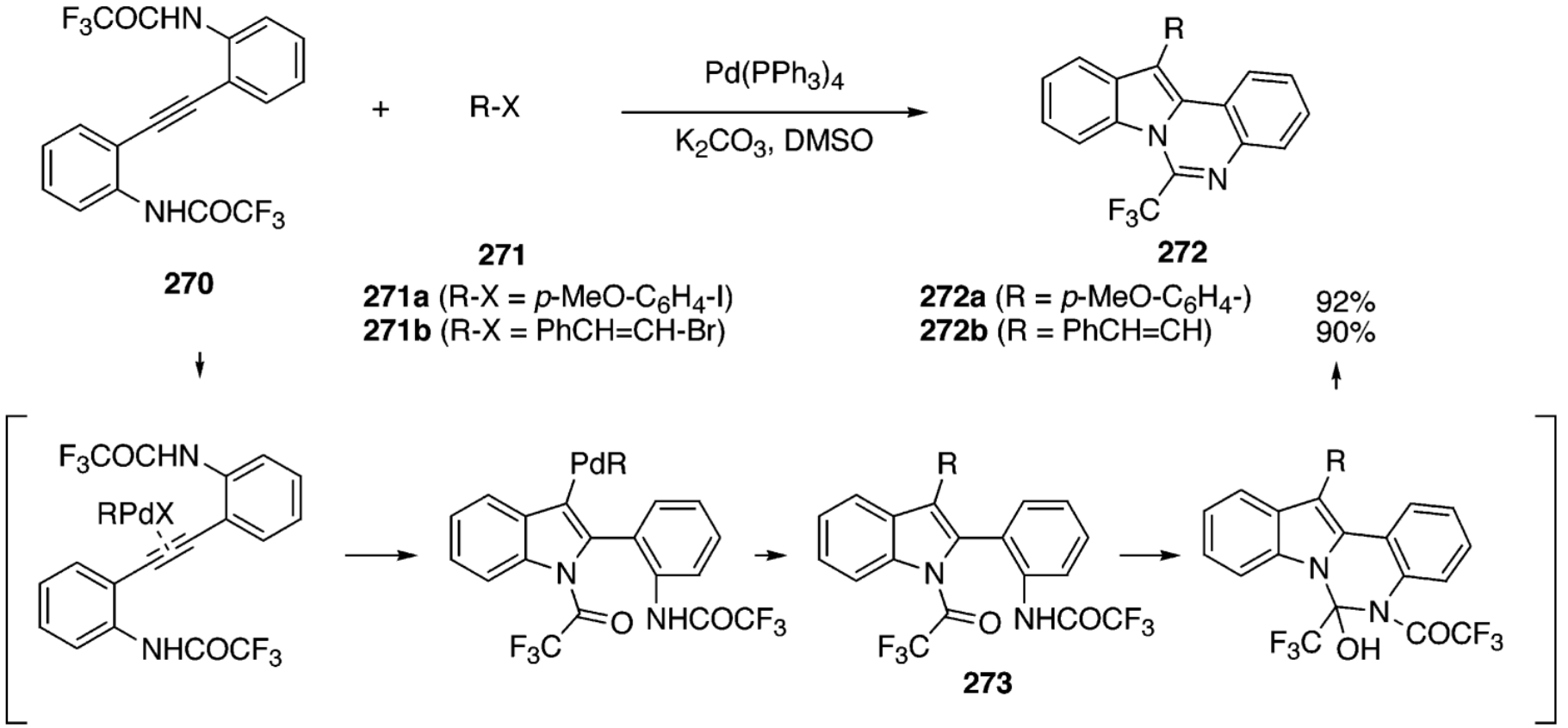
Synthesis – Transition Metal Catalysis

- Nucleophilic cyclisations onto **palladium-complexed alkenes** have been used to prepare indoles, benzofurans and other fused systems

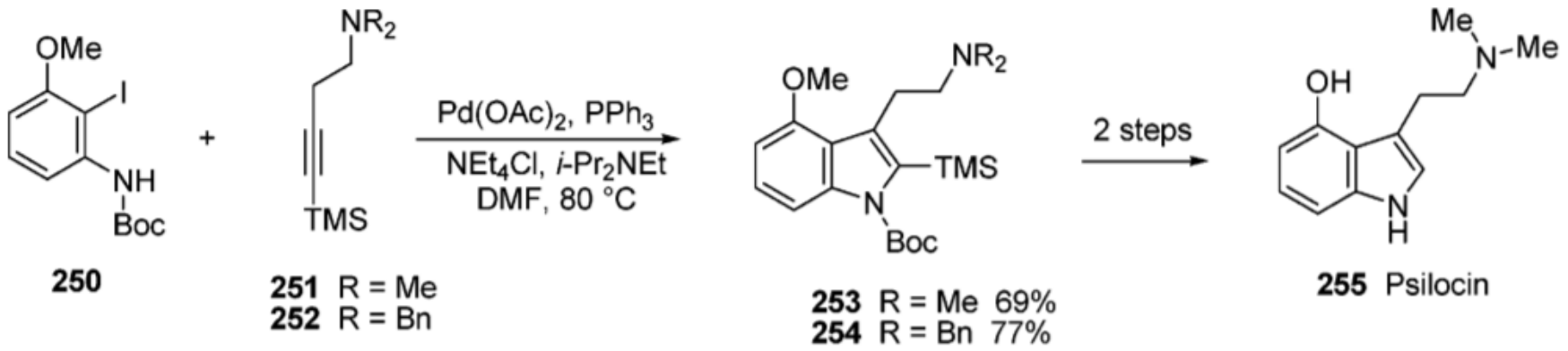


- The process can be made catalytic in some cases by the use of reoxidants such as p-benzoquinone or copper(II) salts

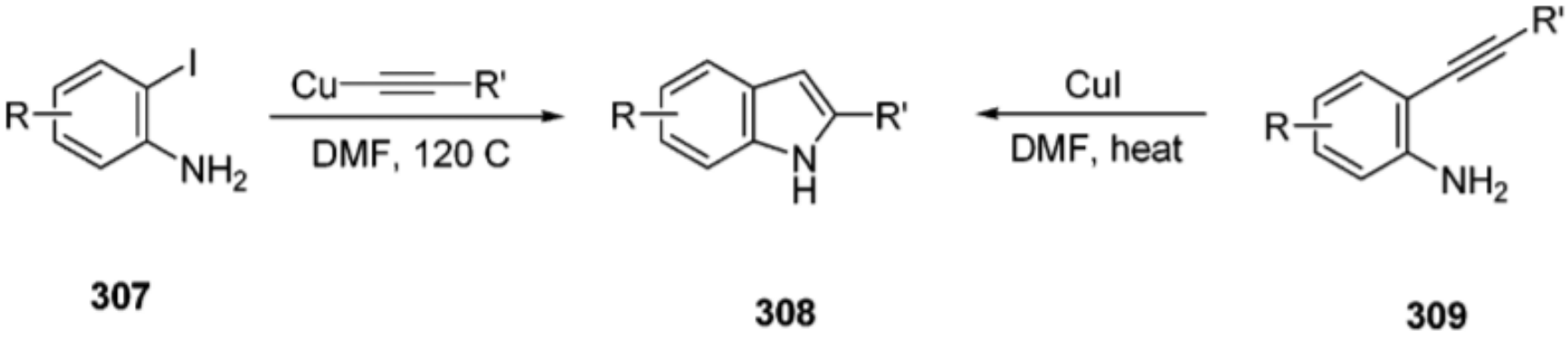
Example:


F3COCHN
NHCOCF3
+
R-X
Pd(PPh3)4
K2CO3, DMSO
R
N
N
F3C
270
271
272
271a (R-X = p-MeO-C6H4-I)
271b (R-X = PhCH=CH-Br)
272a (R = p-MeO-C6H4-) 92%
272b (R = PhCH=CH) 90%
RPdX
PdR
O
NHCOCF3
273
OH
COCF3

Example:

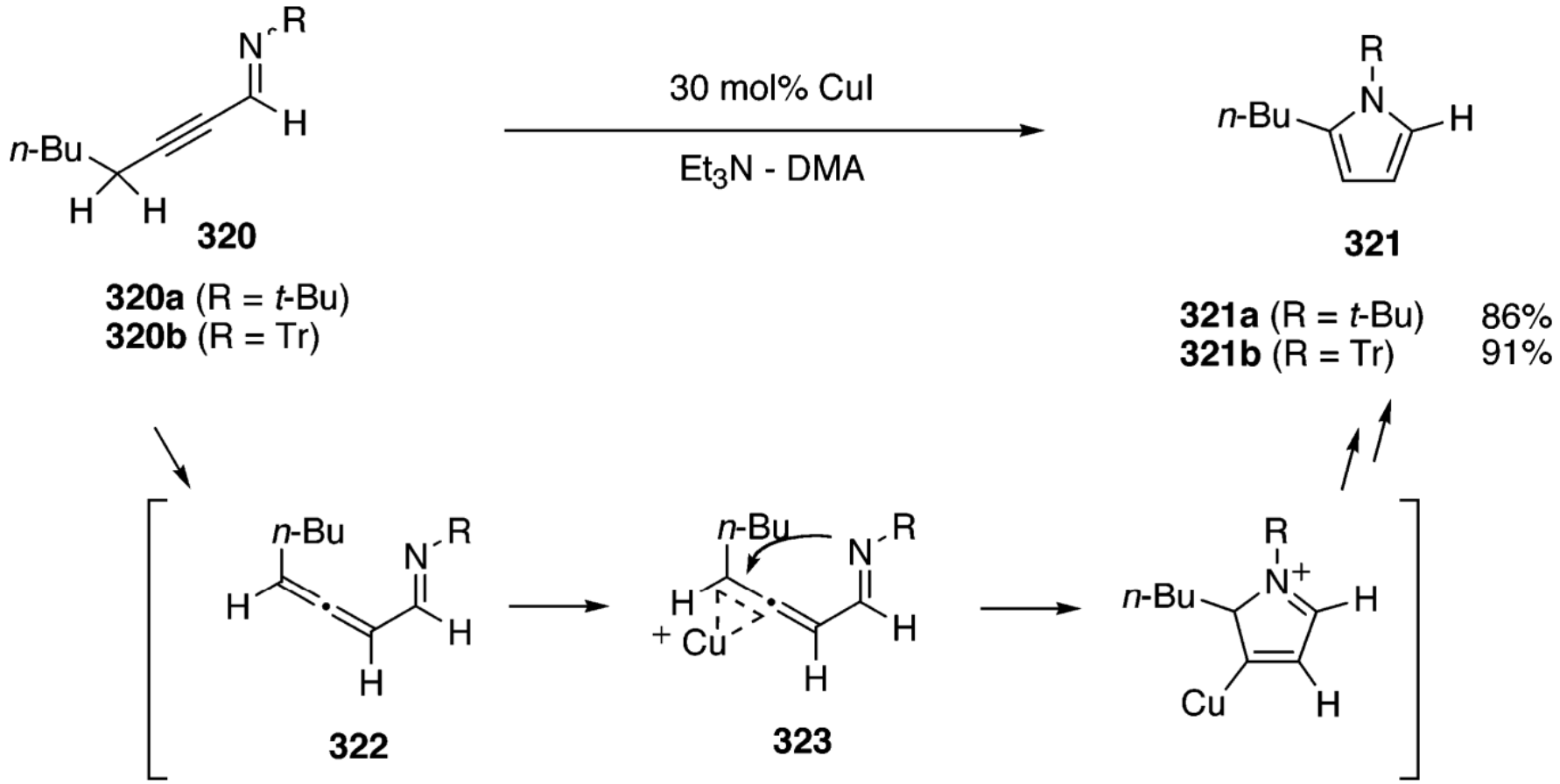

OMe
I
NH
Boc
250
+
NR2
TMS
251 R = Me
252 R = Bn
Pd(OAc)2, PPh3
NEt4Cl, i-Pr2NEt
DMF, 80 °C
OMe
NR2
TMS
N
Boc
253 R = Me 69%
254 R = Bn 77%
2 steps
Me
N-Me
OH
N
H
255 Psilocin

Example:



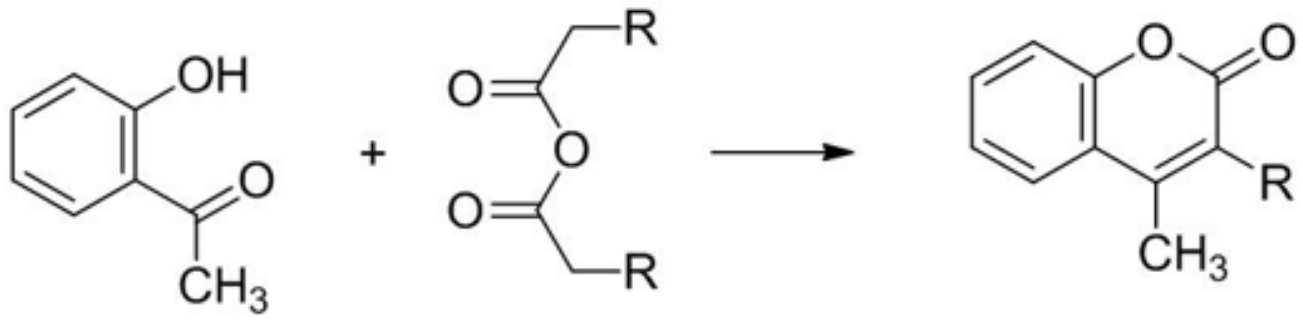
307 **308** **309**

Example:


30 mol% CuI
Et3N - DMA
n-Bu
R
N
H
320
320a (R = t-Bu)
320b (R = Tr)
321
321a (R = t-Bu) 86%
321b (R = Tr) 91%
322
323
Cu

Homework #1 – Kostanecki Acylation

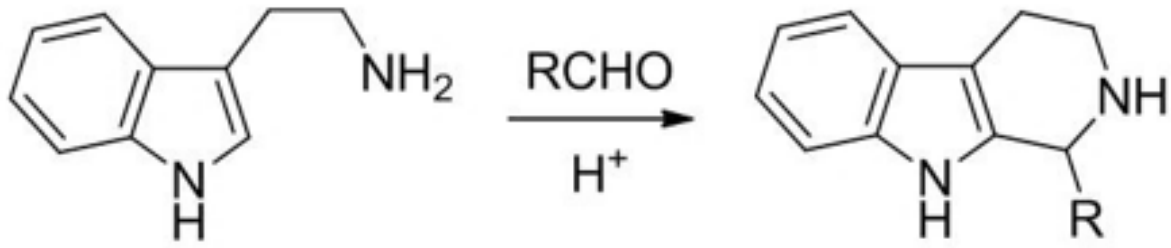
A synthesis of coumarins by acylation of *O*-hydroxyaryl ketones with aliphatic acid anhydrides, followed by cyclization. Developed by Kostanecki in 1901



Provide the mechanism

Homework #2 – Pictet-Spengler Reaction

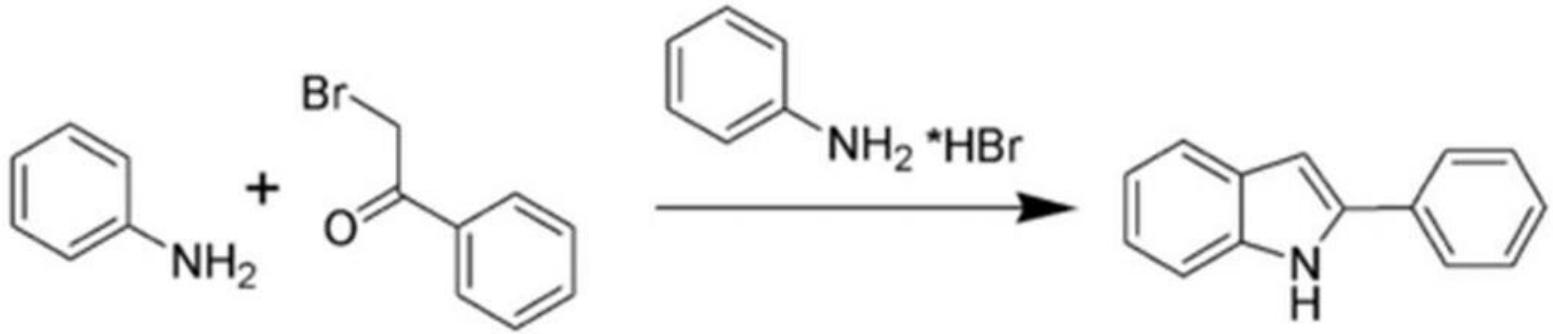
β-Aryl ethylamine (Tryptamine in this case) undergoes acid-cayalyzed ring-closure with aldehyde (a type of Mannich reaction invented in 1911 by Ame Pictet and Theodor Spengler). It is still important for the fields of alkaloids and pharmaceutical synthesis



Provide the mechanism

Homework #3 – Bischler-Möhlau Indole Synthesis

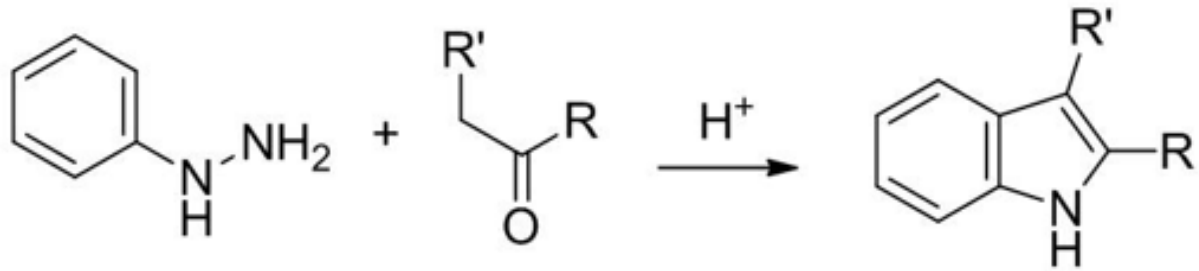
Named after August Bischler and Richard Möhlau. It forms a 2-aryl-indole from an *α*-bromo-acetopheneone and excess aniline under a harsh conditions.



Provide the mechanism

Homework #4 – Fischer indole synthesis

Discovered in 1883 by Emil Fischer, produces indole derivative from a phenylhydrazine and an aldehyde or a ketone under acidic conditions. Nowadays, Antimigrane drugs are often synthesized by this method.



Provide the mechanism