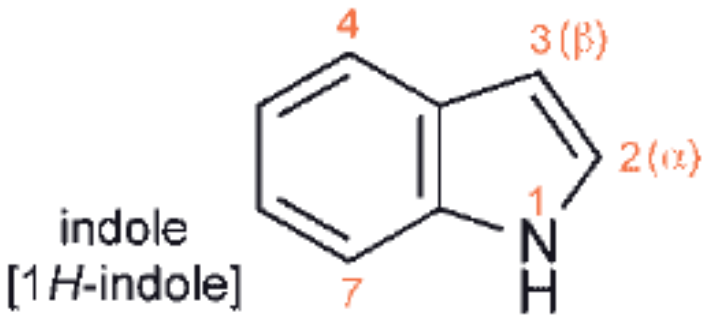
Unit-III

Benzo-fused five membered heterocycles

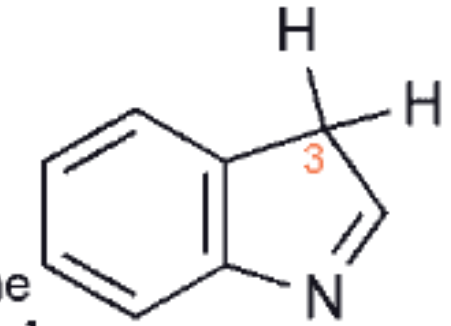
By

Siddharth Sharma

Synthetic methods, physical and chemical properties of benzopyrroles, benzofuranes and benzothiophenes.



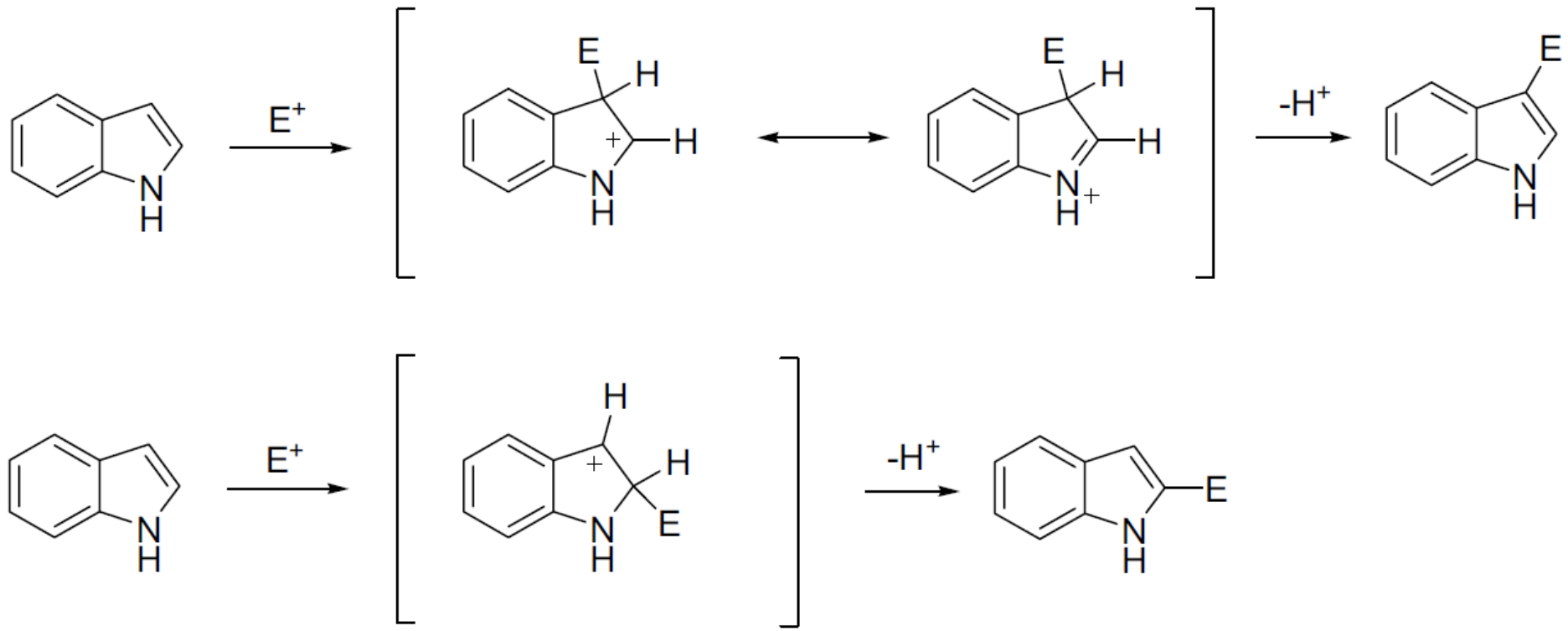
indole
[1*H*-indole]



indolenine
[3*H*-indole]

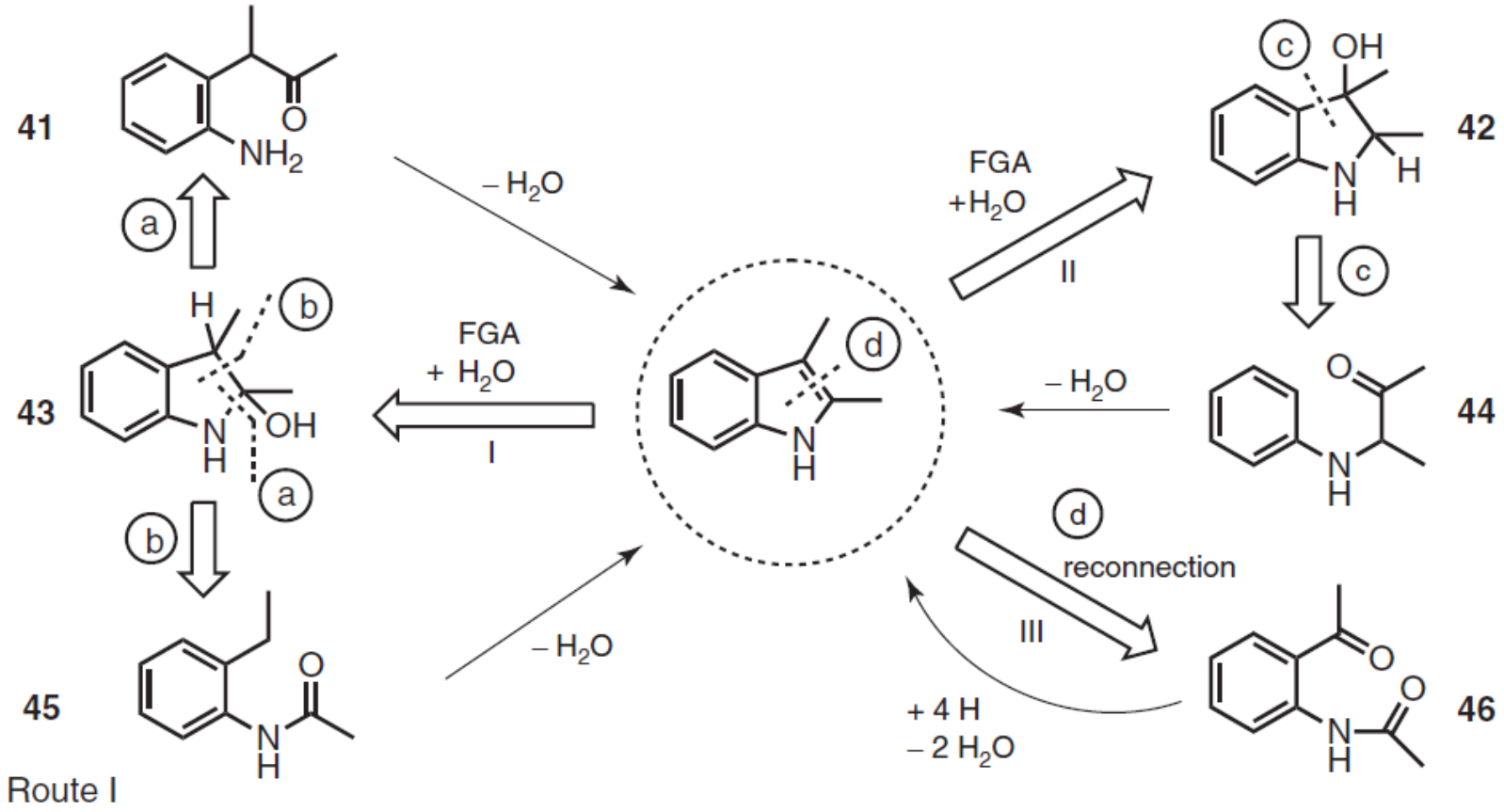
The word indole is derived from the word India: a blue dye imported from India was known as indigo in the sixteenth century. indole itself was first prepared in 1866 by zinc - dust distillation of oxindole.

Indole is a crystalline solid (mp=54–54 C, bp=253–254 C). The main commercial source of indole comes from the 220–260 C fraction of coal-tar distillation. It is soluble in organic solvents such as diethyl ether, ethanol and benzene, and also in hot water.

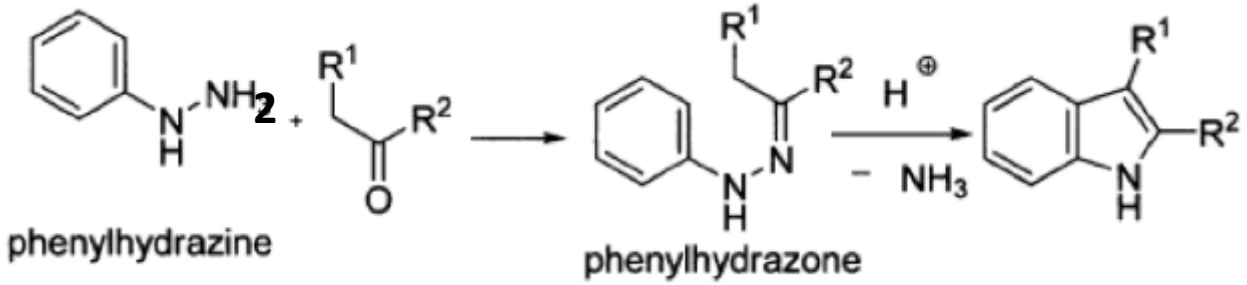


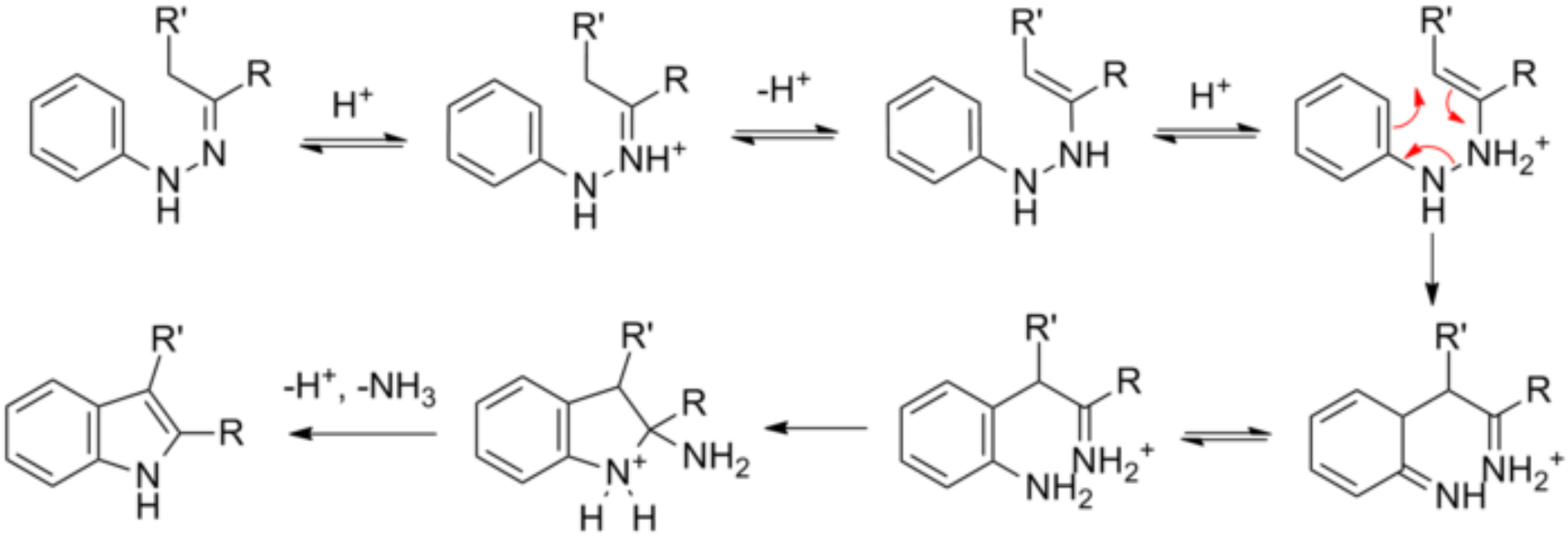
Scheme 5.1 Possible regioisomers in the electrophilic attack on the indole ring.

Retrosynthesis of indole

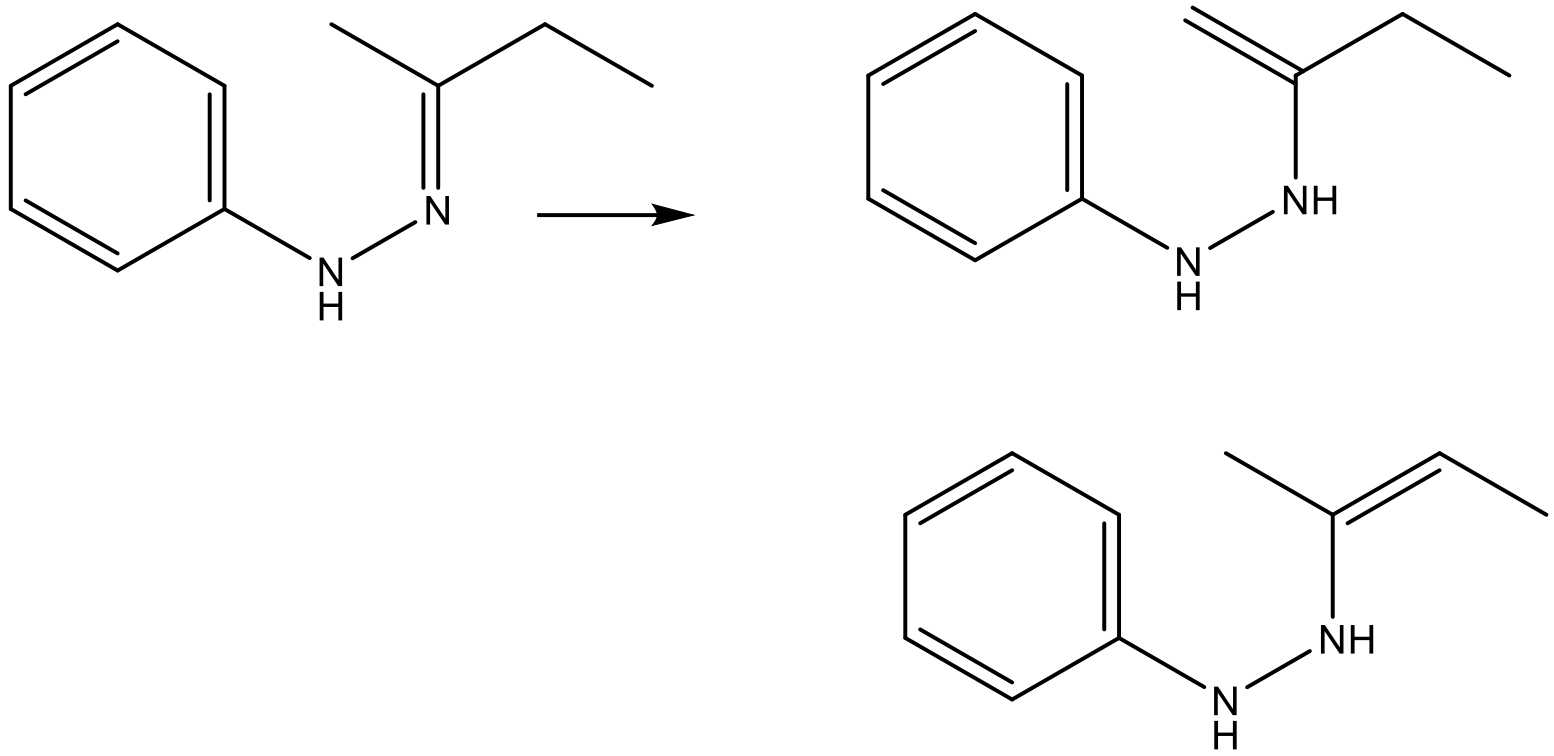


Fischer Indole Synthesis

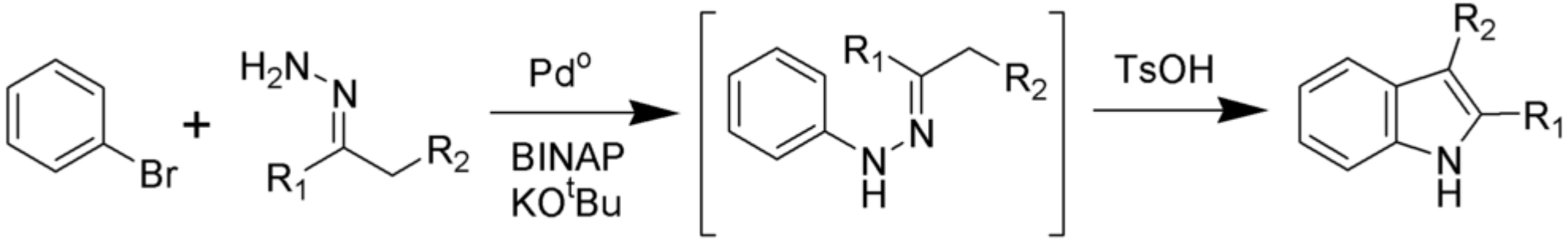




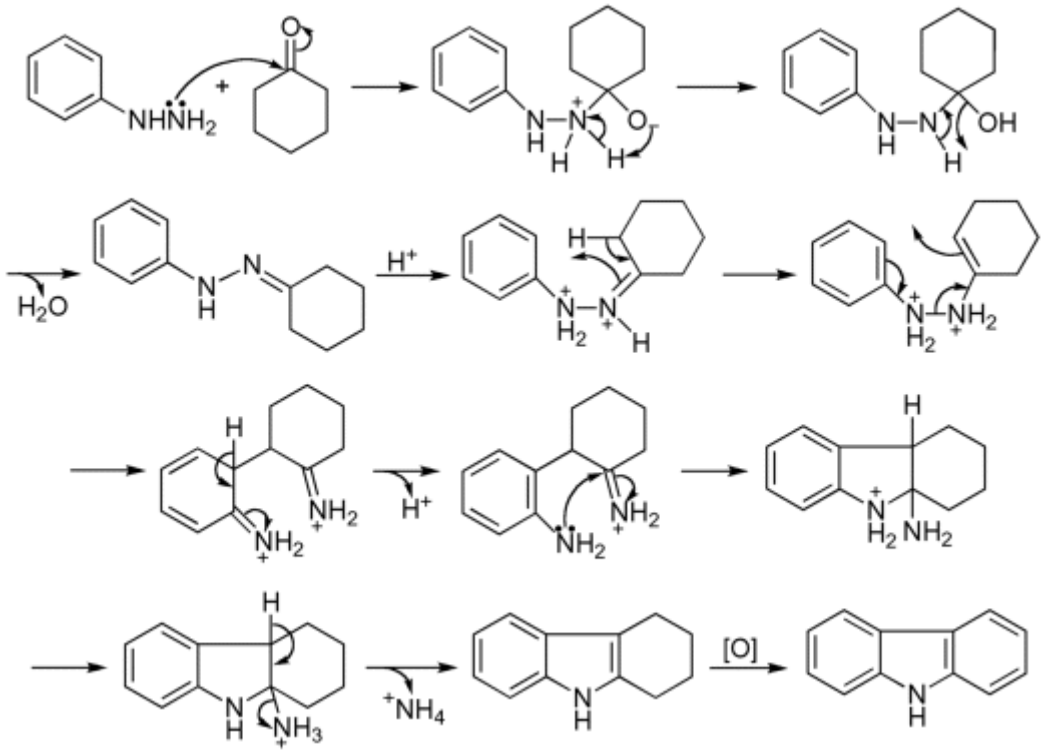
(3,3)-sigmatropic rearrangement (diaza-Cope rearrangement).


N
H
N
NH
N
H
NH
N
H

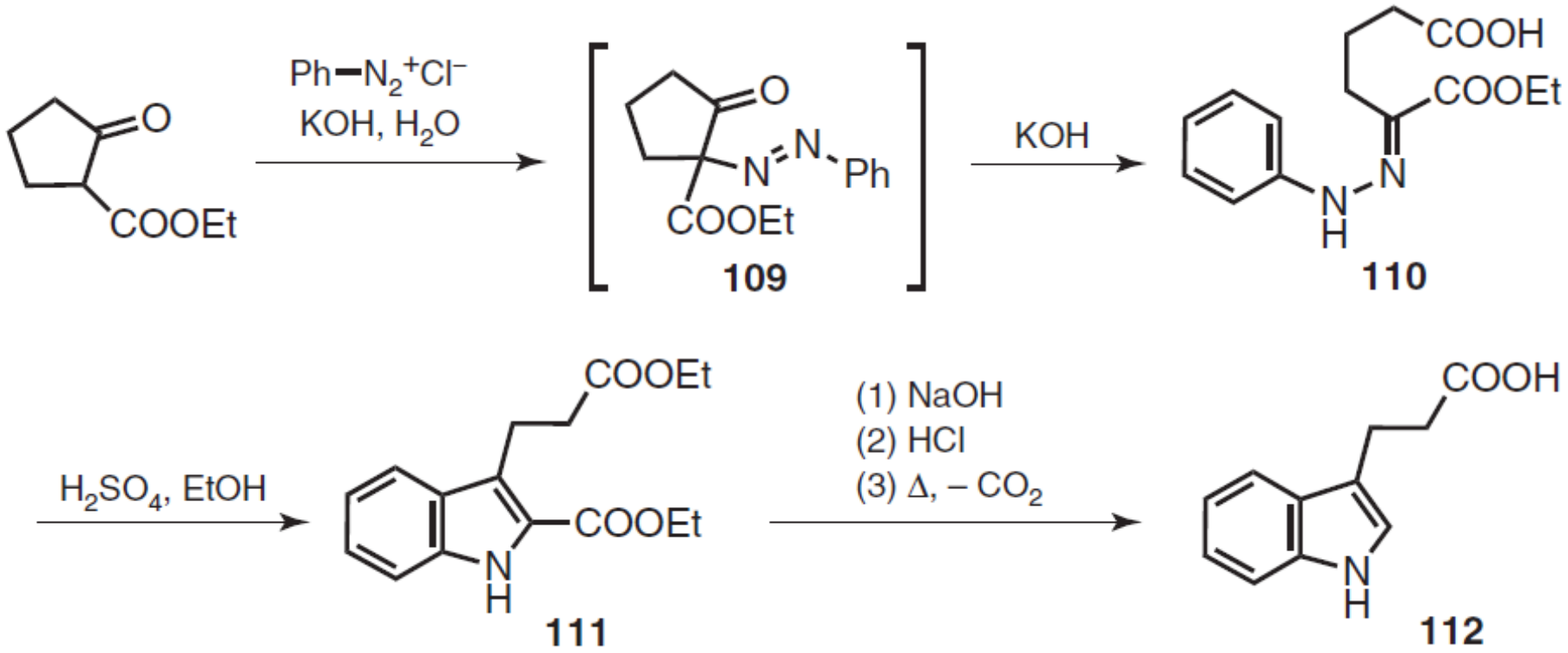
Variant in Fischer Indole Synthesis



Borsche-Drechsel Reaction

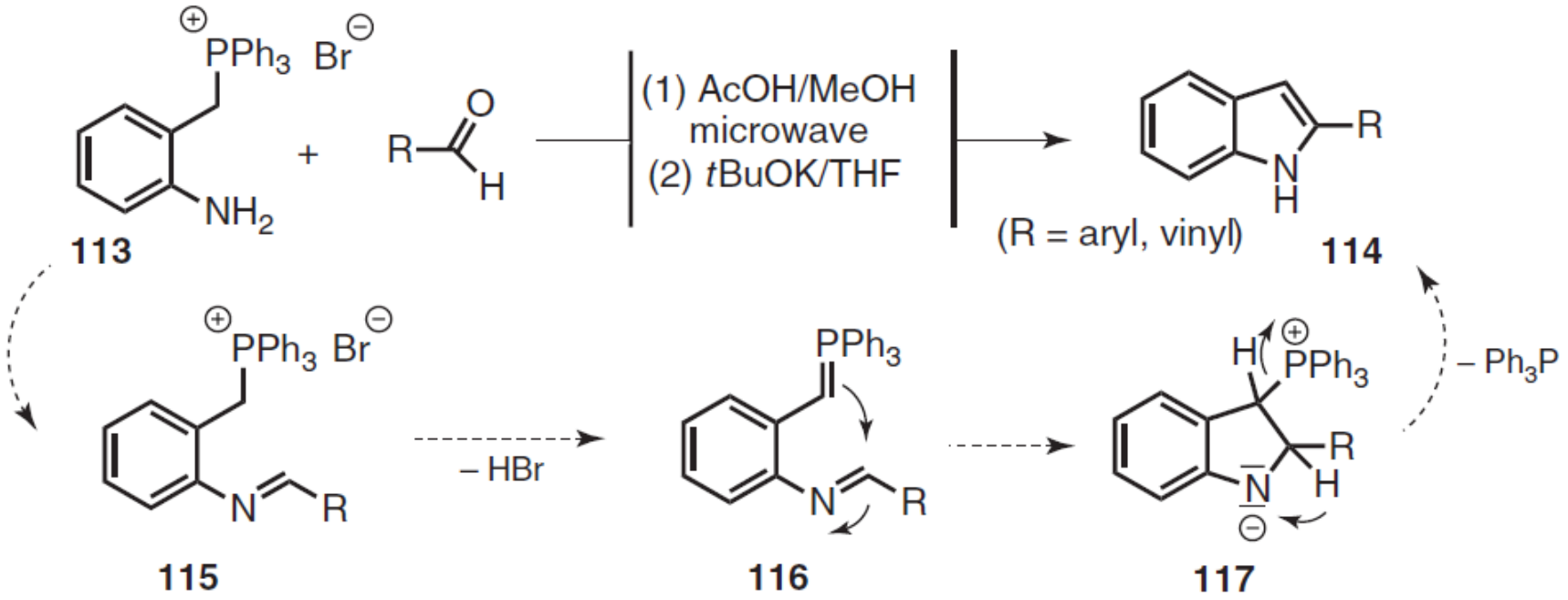


Variant in Fischer Indole Synthesis

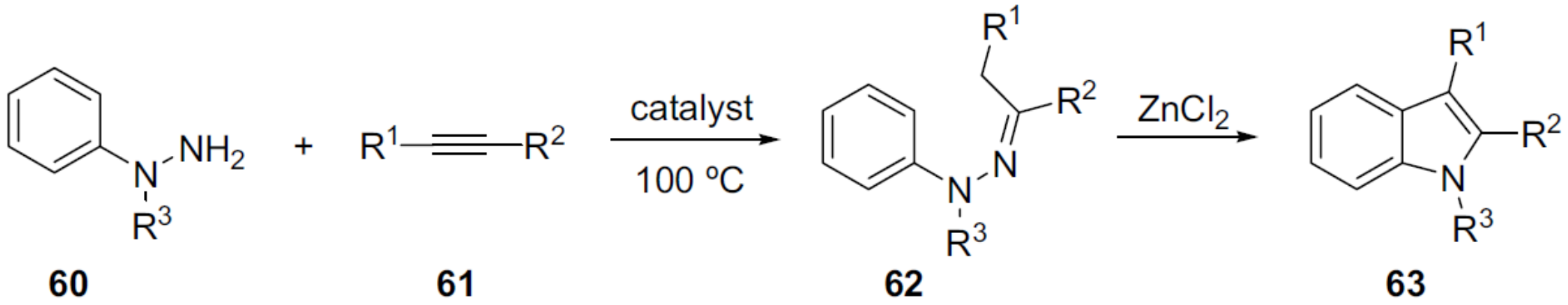


Variant in Fischer Indole Synthesis

(2-Aminobenzyl)phosphonium salts **113** and aromatic or α,β-unsaturated aldehydes can be transformed to 2-aryl-or 2-vinyl indoles **114** in a two-step one-pot procedure



Variant in Fischer Indole Synthesis

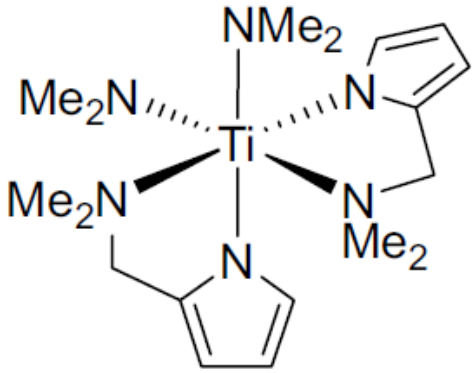


60 **61** **62** **63**

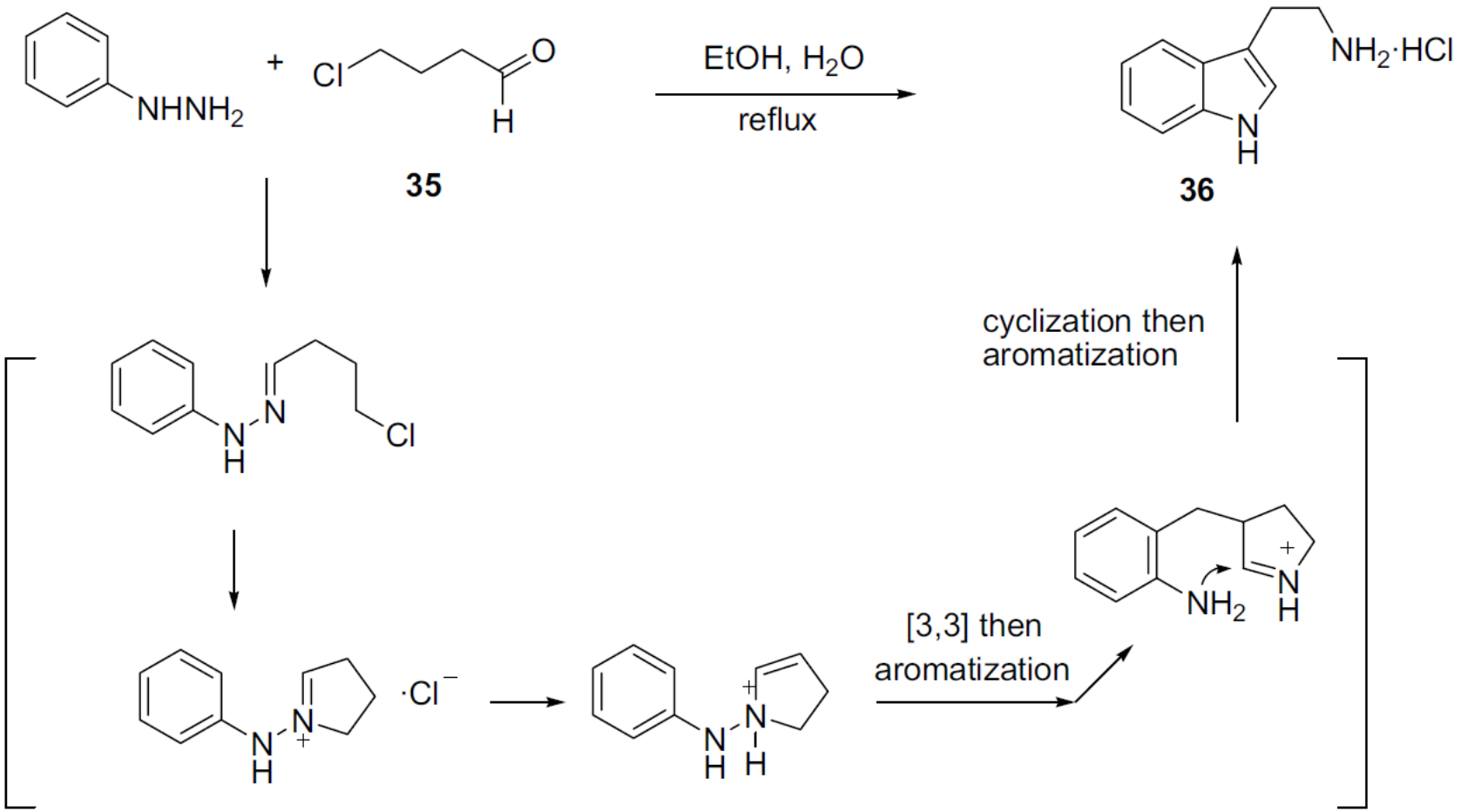
56-95%

R^1, R^2 = H, Ar, Alkyl

Catalyst:

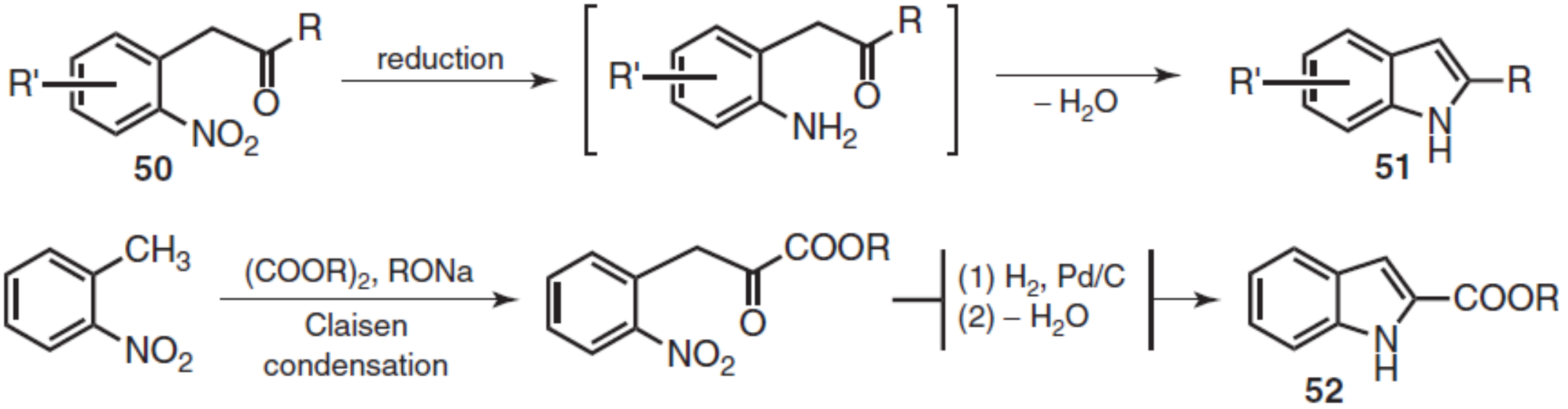


Variant in Fischer Indole Synthesis

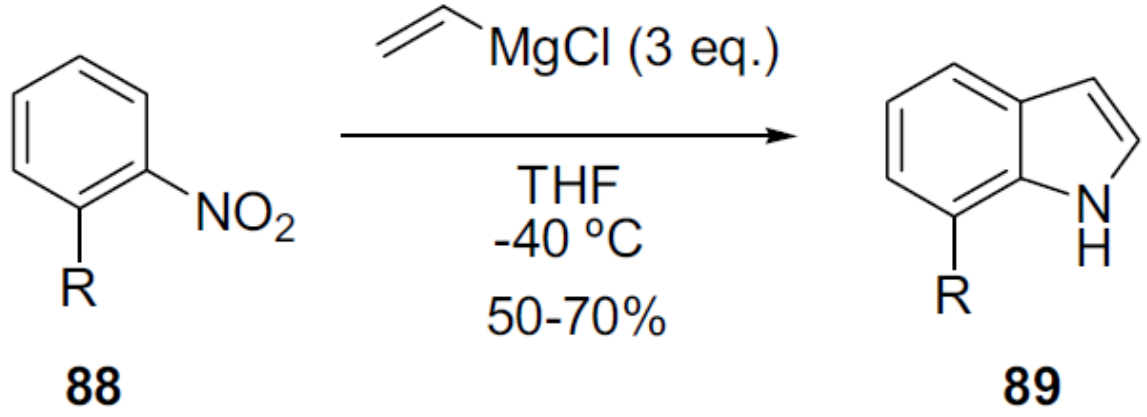


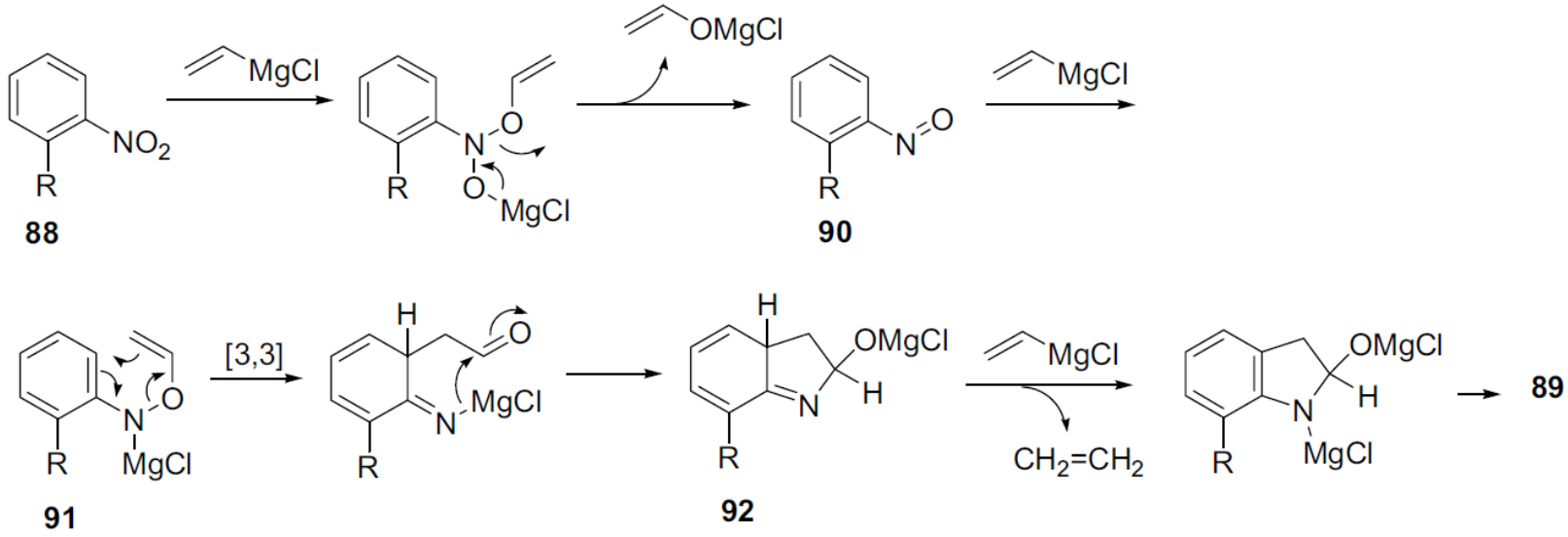
Scheme 5.20 Grandberg indole synthesis.

Reissert synthesis



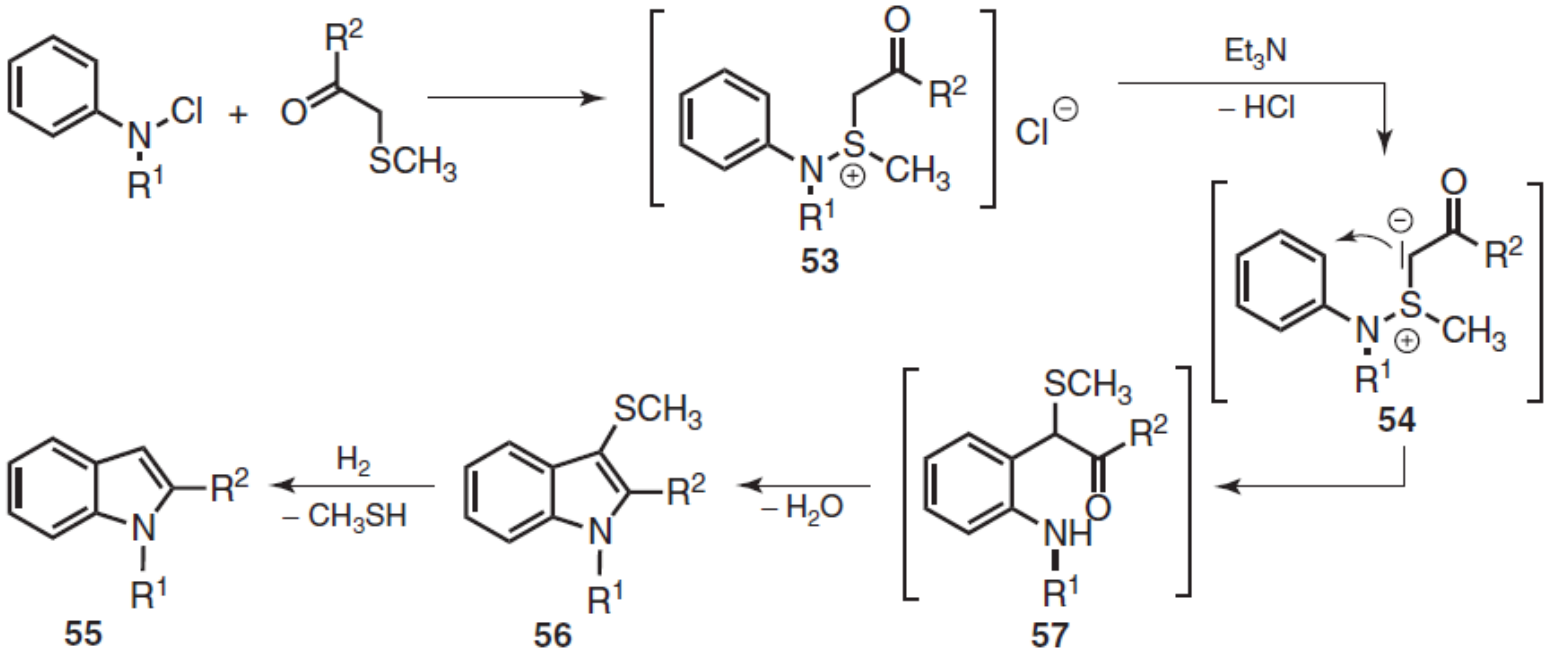
Bartoli Synthesis





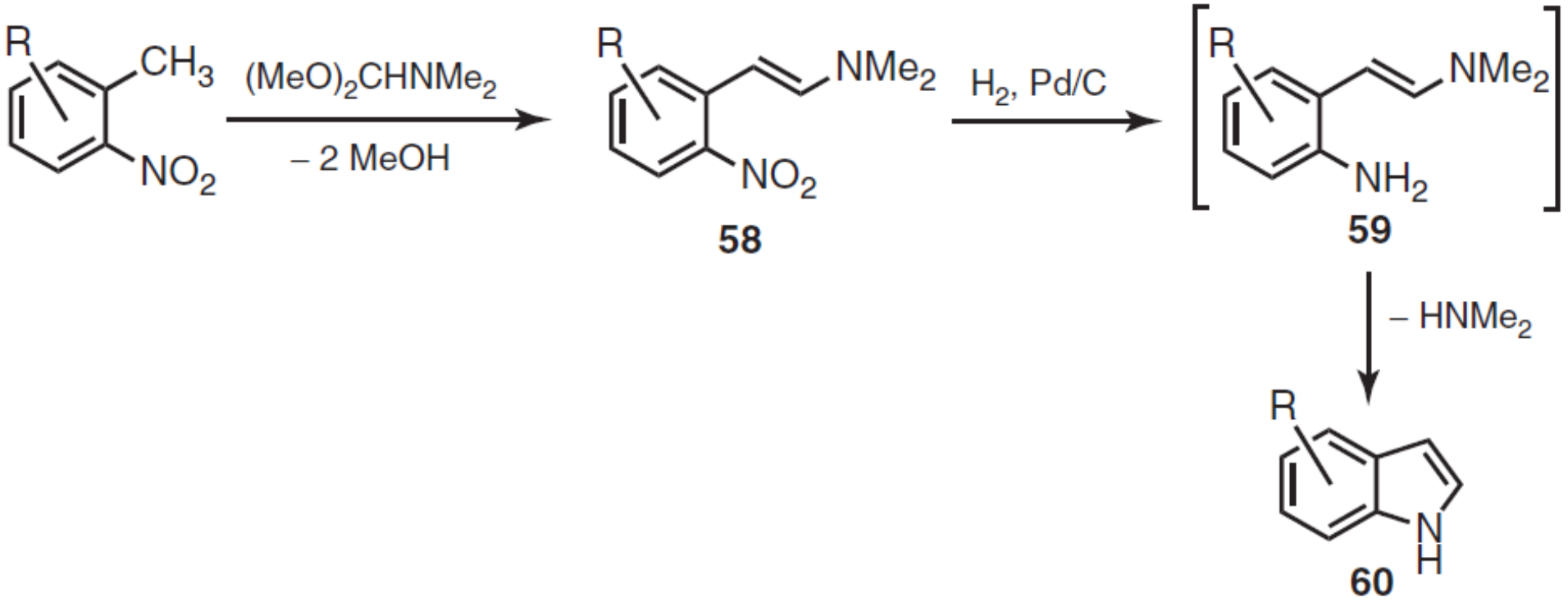
Gassmann synthesis

(o-Aminobenzyl) carbonyl compounds are also formed from *N*-chloroanilines and α-(methylsulfanyl) ketones via anilinosulfonium salts **53**

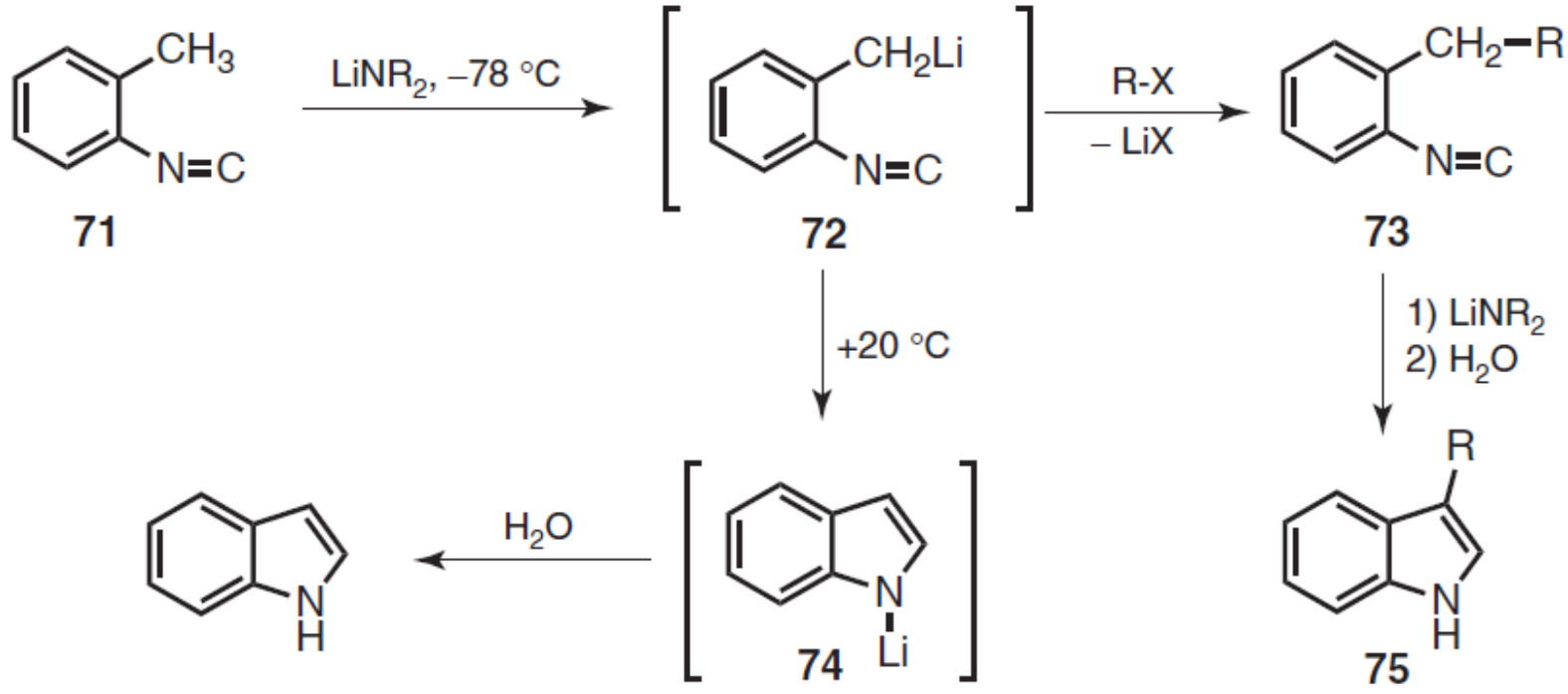


Batcho-Leimgruber synthesis

1-Dimethylamino-2-(o-nitrophenyl)ethenes **58**, obtained by condensation of o-nitrotoluene with *N,N*-DMF dimethylacetal, undergo reductive cyclization (via the o-aminomethyl derivative **59**) to indoles **60** on catalytic hydrogenation

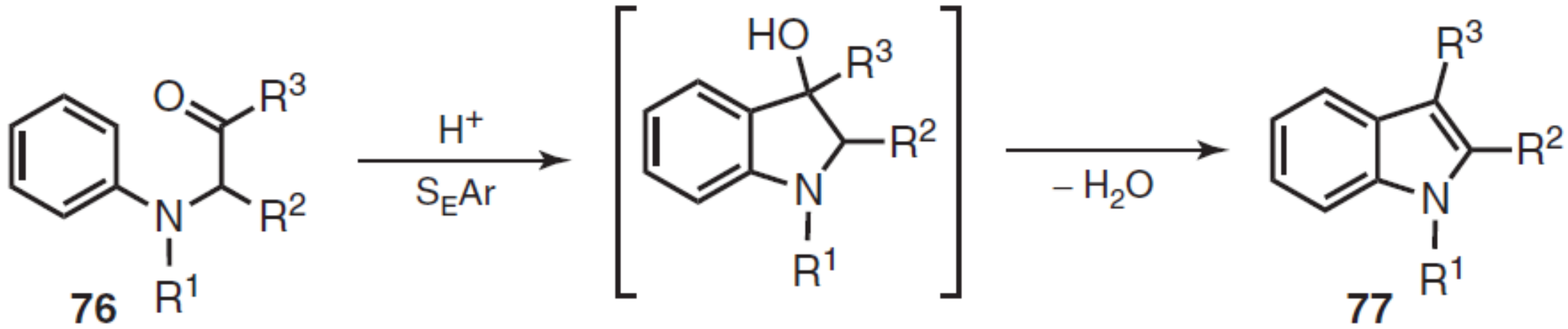


Madelung synthesis



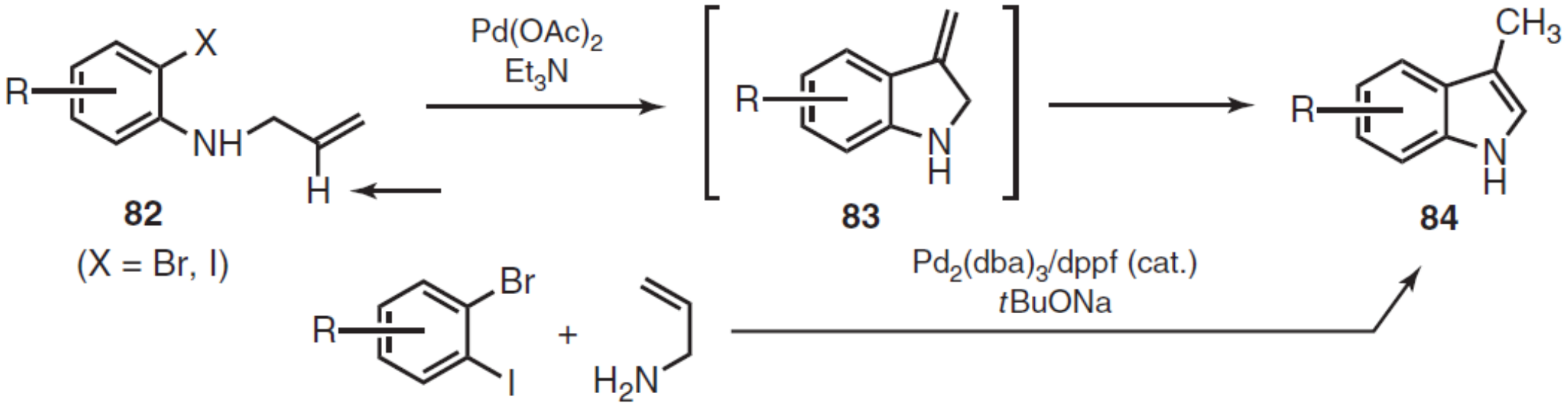
Bischler synthesis

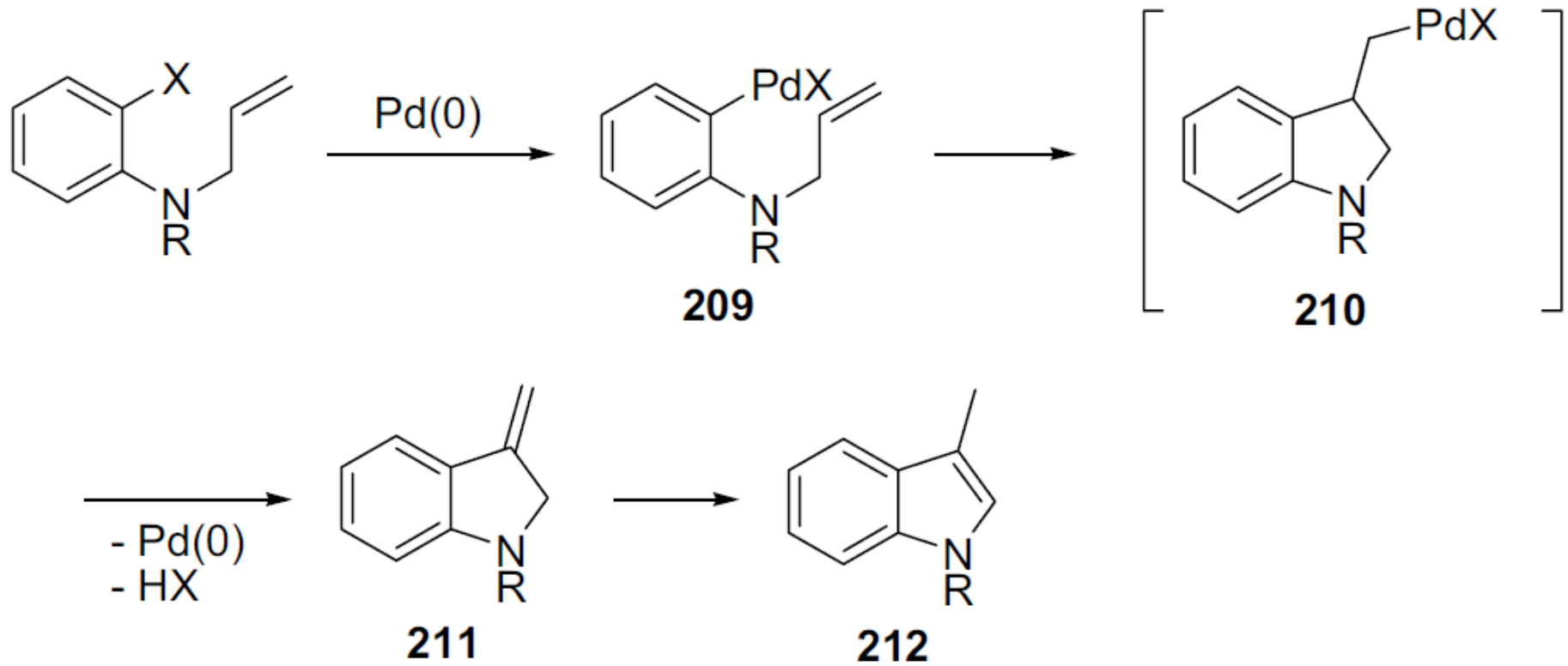
α-Arylaminoketones **76**, easily accessible from arylamines and α-halogenoketones, are cyclized to indoles **77** on treatment with strong acids by intramolecular SEAr reaction and subsequent H2O elimination



Intramolecular Heck reactions

(*N*-Allyl)-2-halogenoanilines, for example, **82,** can be cyclized under catalysis of $Pd(OAc)_2$ and in the presence of triethylamine to give 3-methylindoles **84.**




X
N
R
Pd(0)
PdX
N
R
209
PdX
N
R
210
- Pd(0)
- HX
N
R
211
N
R
212

Nenitzescu synthesis