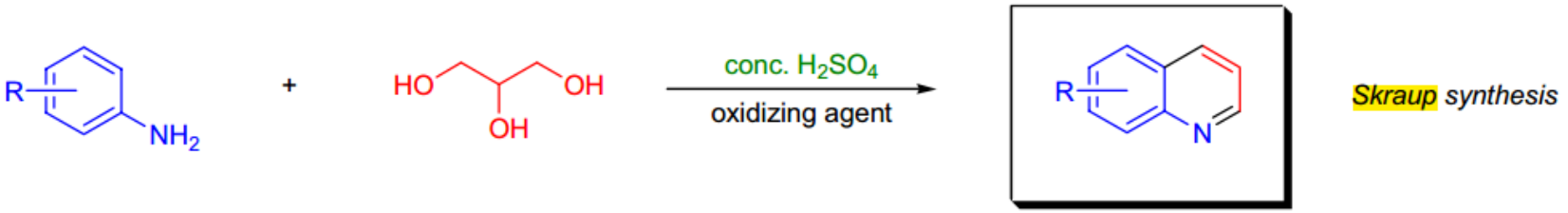
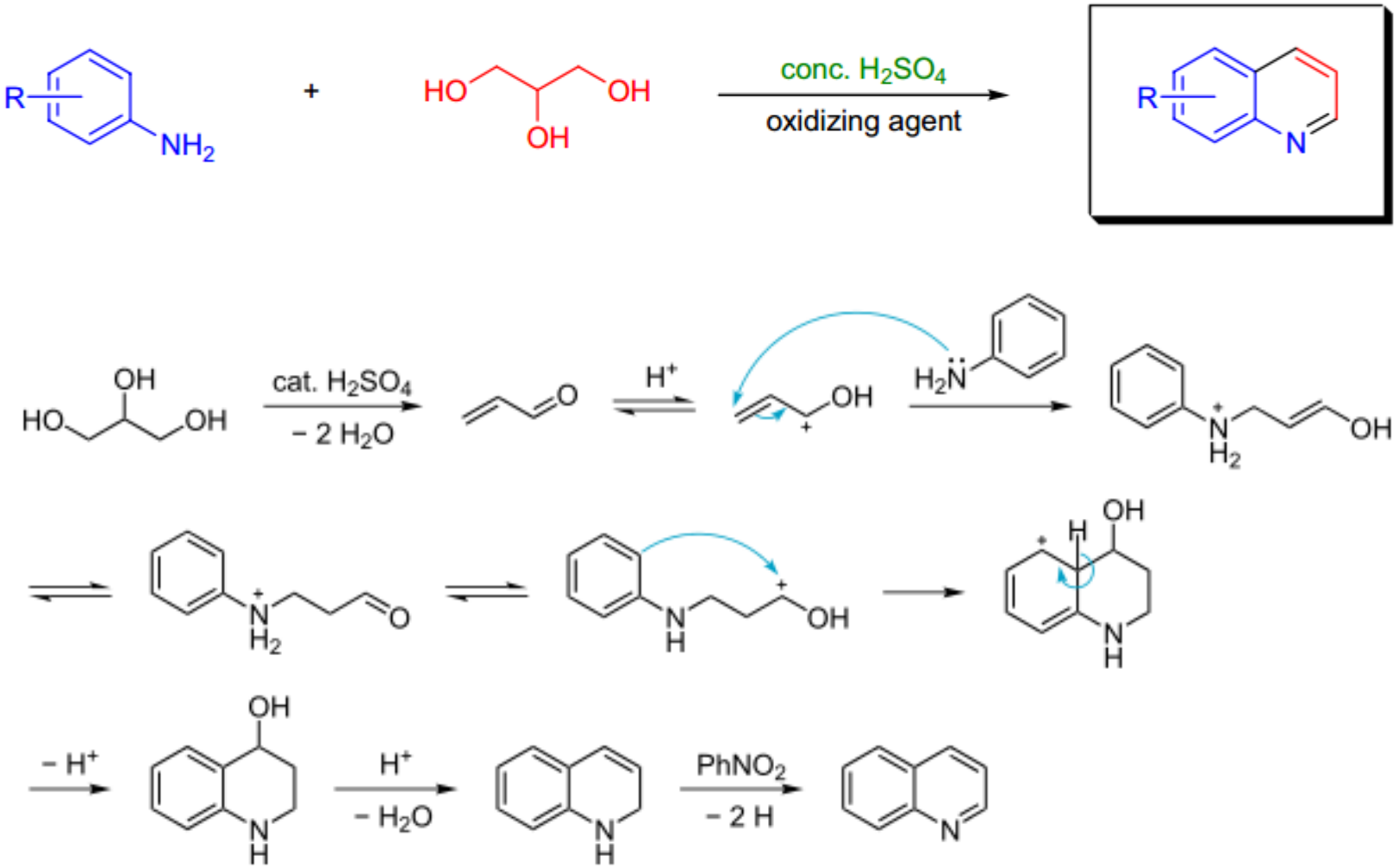
Skraup and Doebner-Miller quinoline synthesis



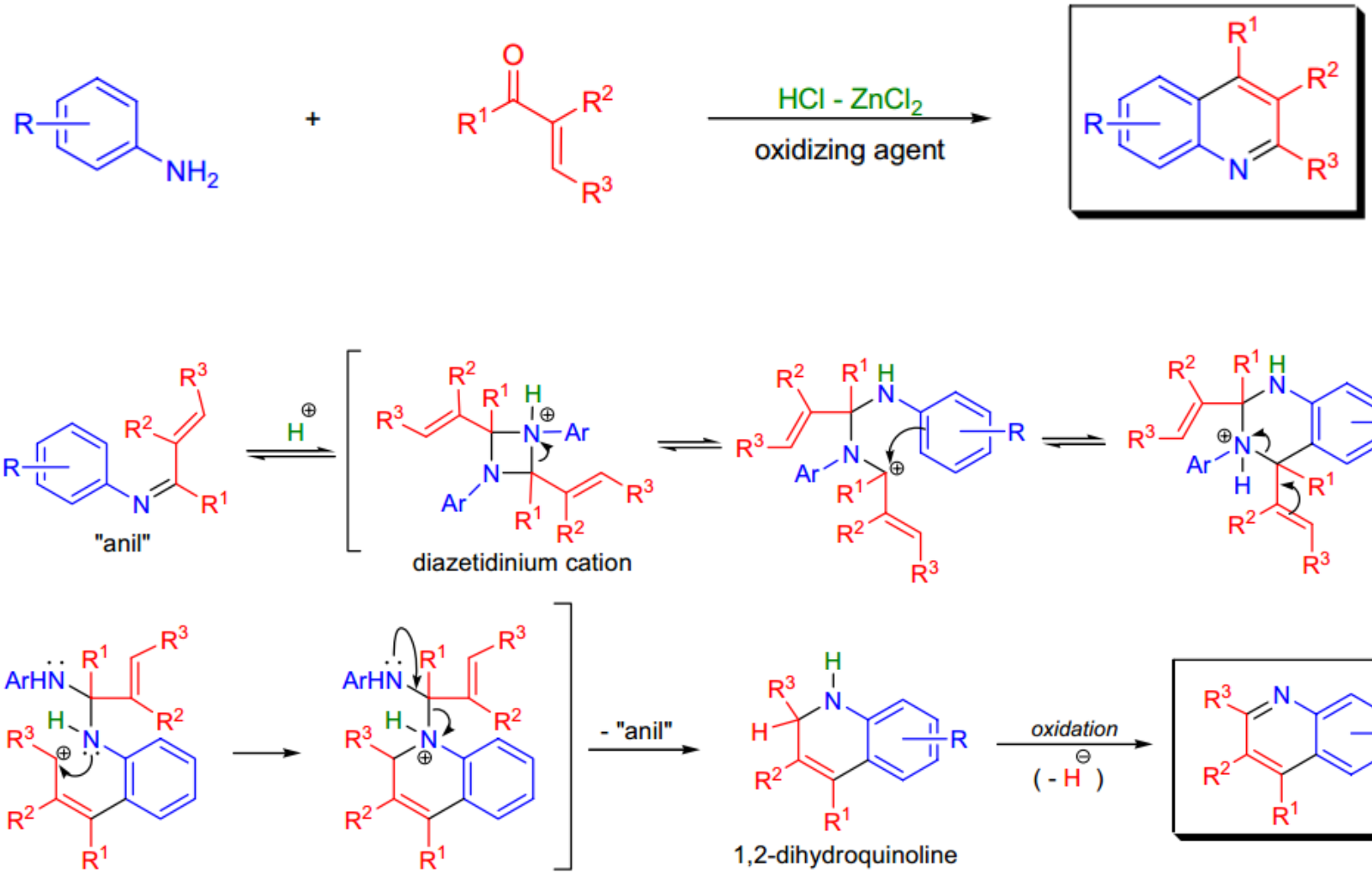
(As_2O_5, $ArNO_2$, *m*-$NO_2C_6H_5SO_3H$, etc.)

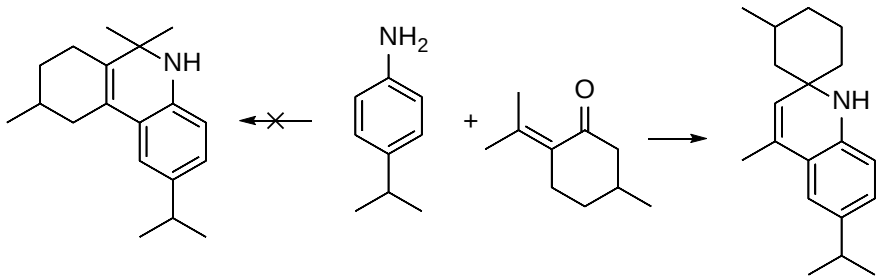
In 1880, Z.H. Skraup （Czech chemist）

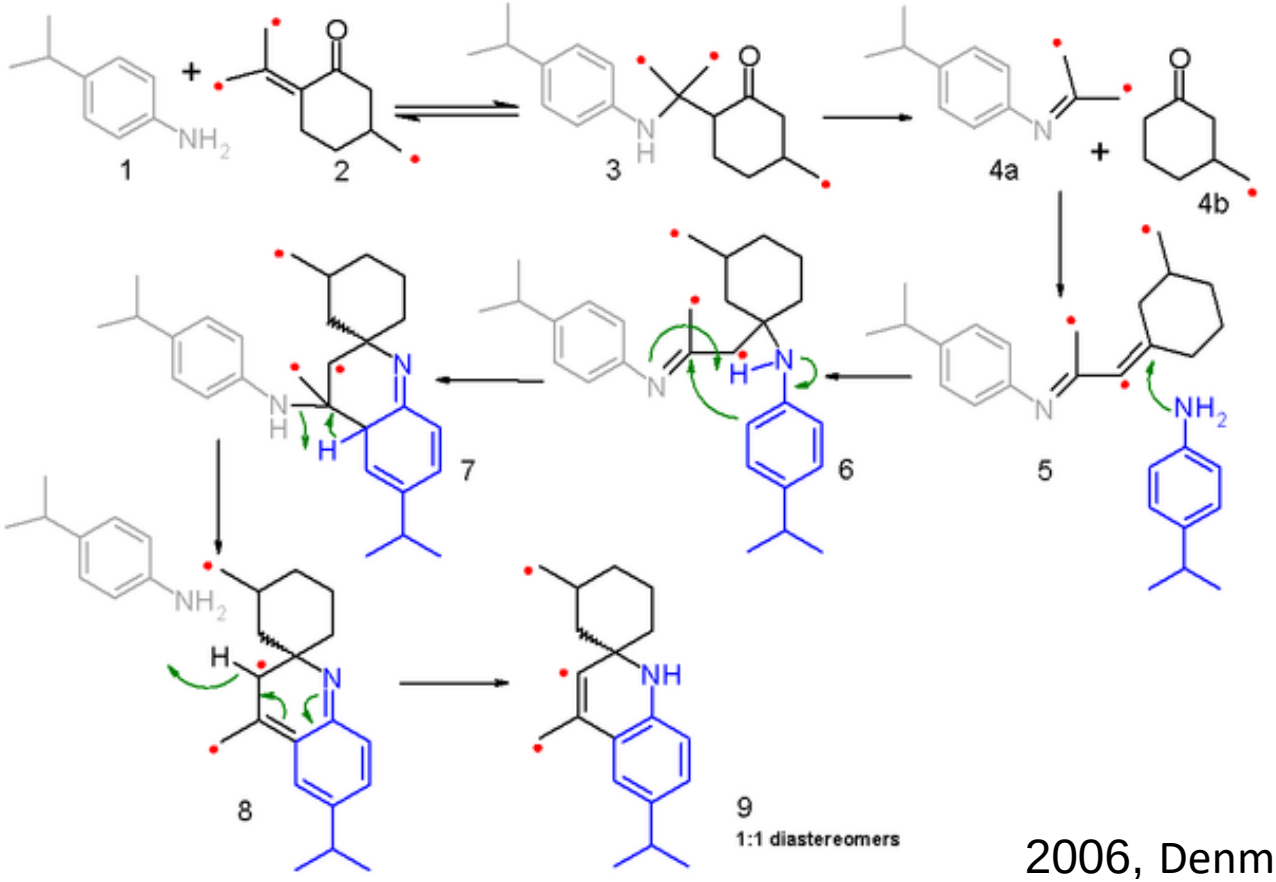


Skraup reaction - Wikipedia
https://en.wikipedia.org/wiki/Skraup_reaction

In 1881, O. Doebner and W. Miller（Czech chemist）

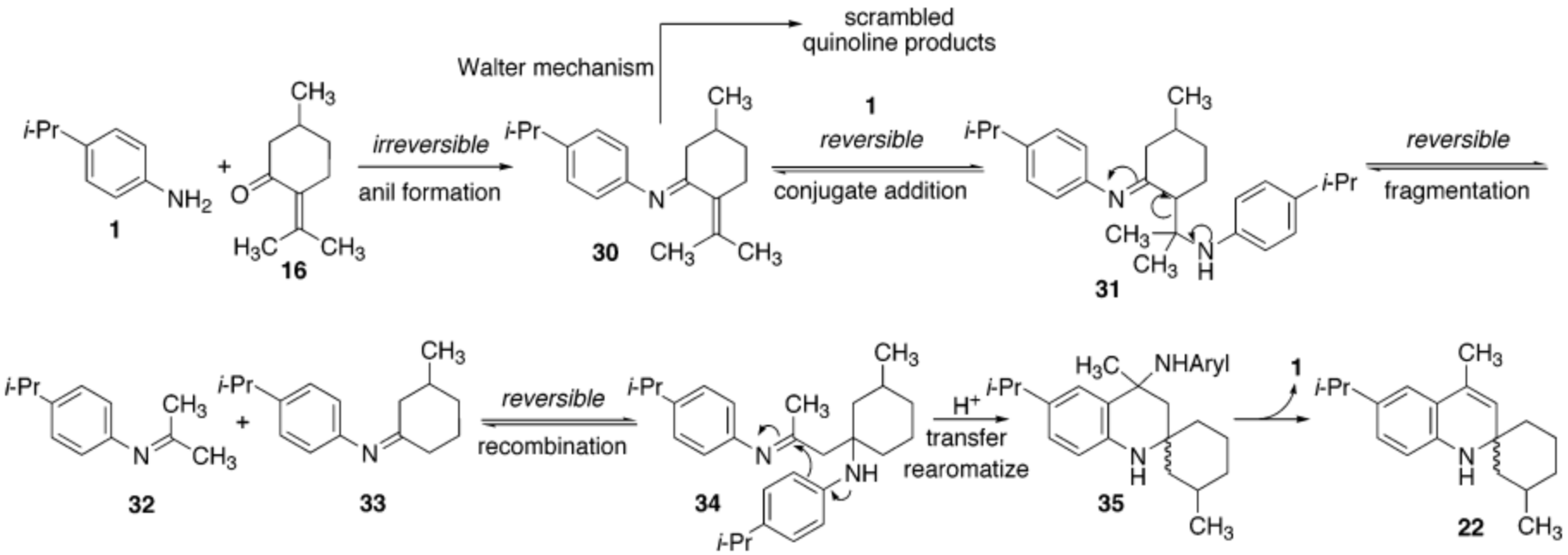






fragmentation-recombination

2006, Denmark, Scott E



J. Org. Chem. **2006**, *71*, 1668-1676

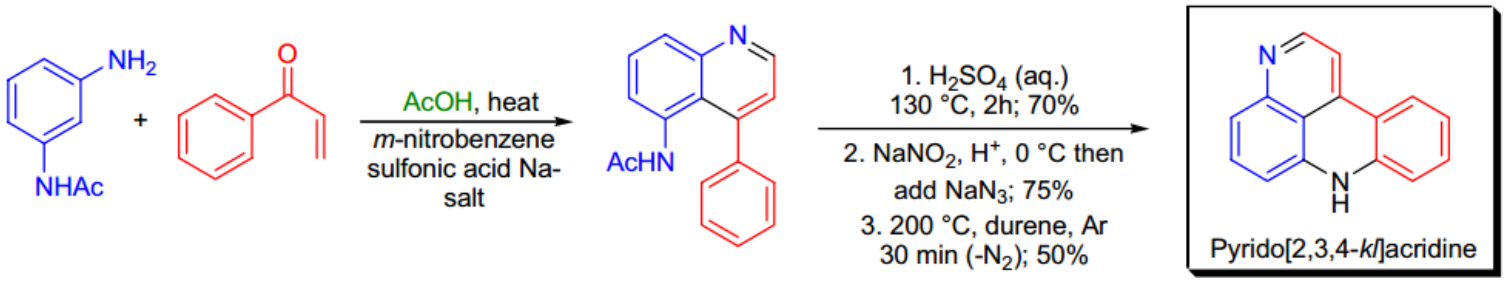
A great advantage：
Structurally complex quinoline derivatives can be prepared in a simple operation.

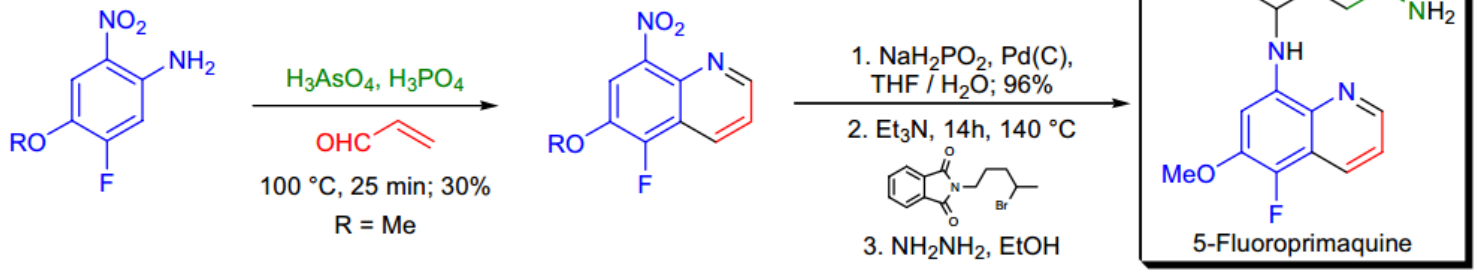
A few drawbacks:
1) the carbonyl component undergoes polymerization under the strongly Lewis acidic conditions; consequently the yields are often **moderate**;
2) the rate of addition of the aldehyde influences the yield;
3) isolation of the product from the complex reaction mixtures is often **tedious**;
4) large-scale reactions are usually **impractical**.

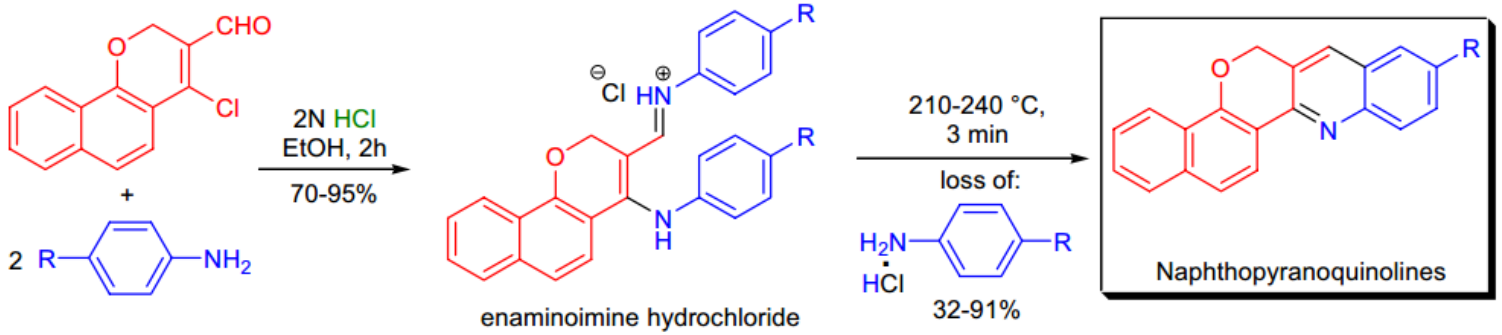
A recent modification of the Doebner-Miller synthesis in a **two-phase solvent system** allows the clean preparation of the desired quinoline derivative on a large scale.

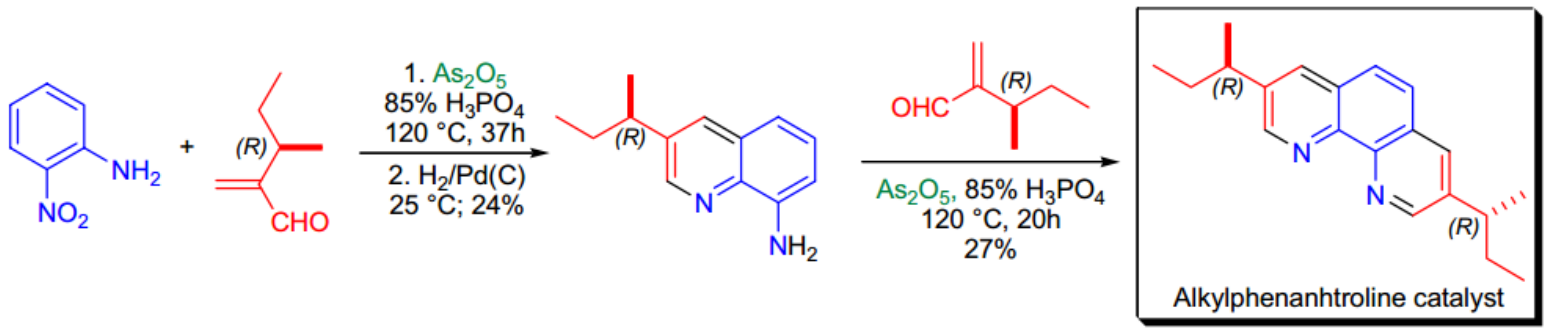
If the aniline substrate is unsubstituted, the oxidizing agent is usually **nitrobenzene**, since it is conveniently converted to aniline in the process.

Synthetic Applications:

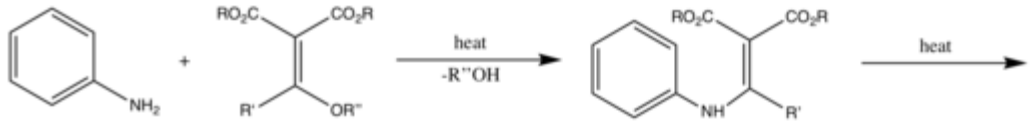


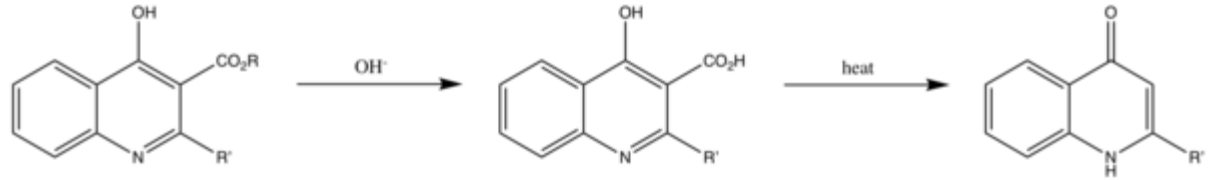




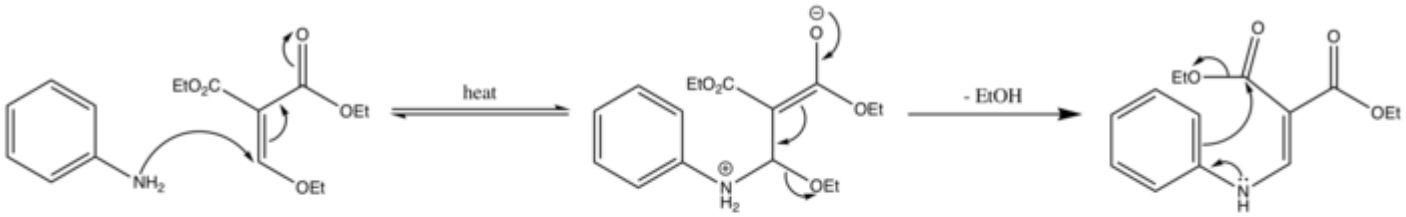


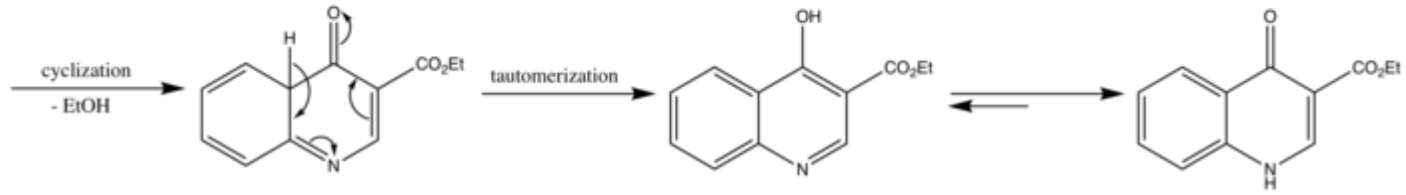
Gould–Jacobs reaction



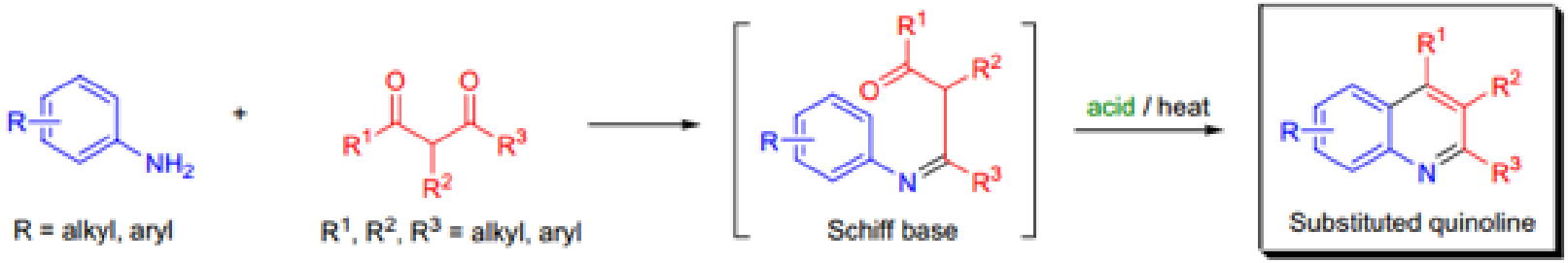


R = alkyl
R' = alkyl, aryl, or H
R" = alkyl or H

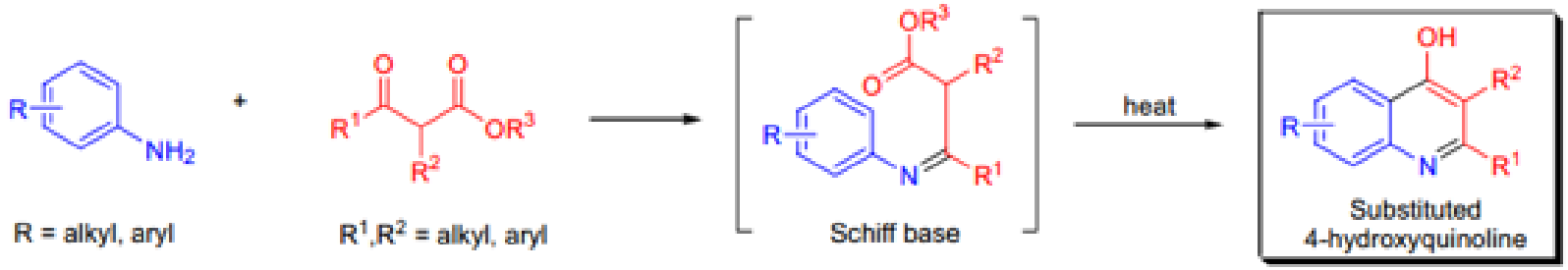




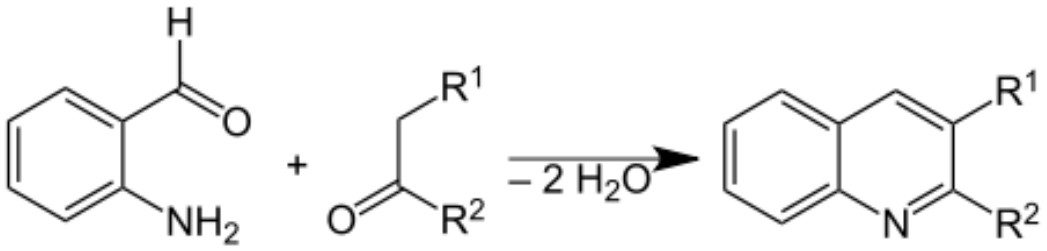
Combes quinolone synthesis



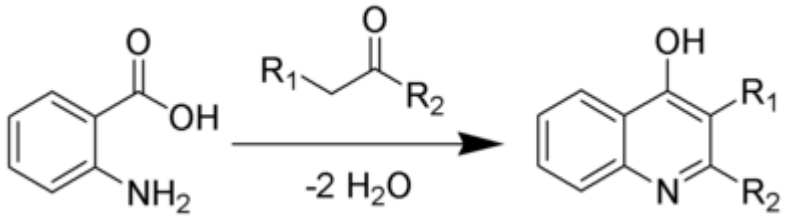
Conrad-Limpach reaction



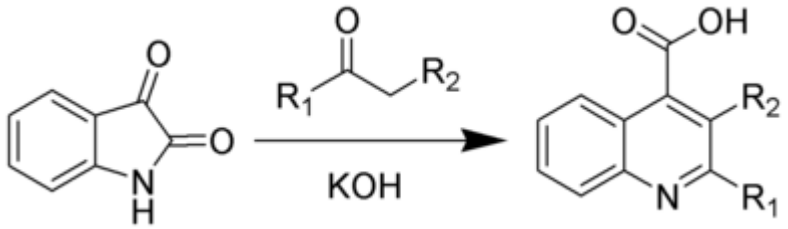
Friedländer synthesis

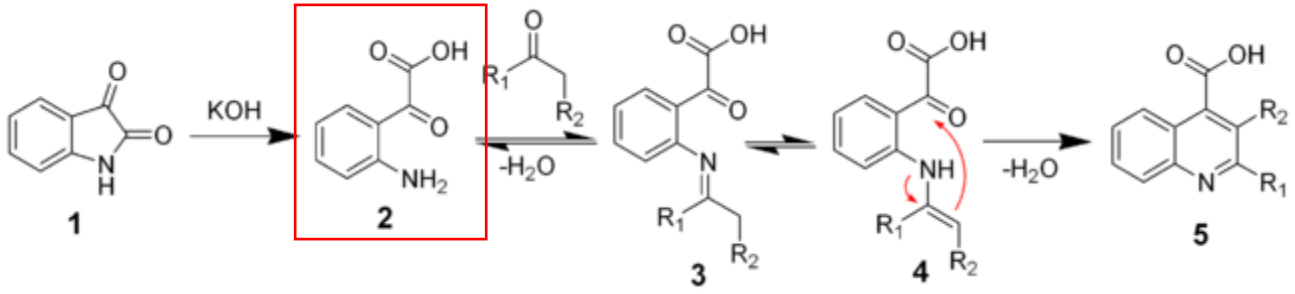


Niementowski quinoline synthesis

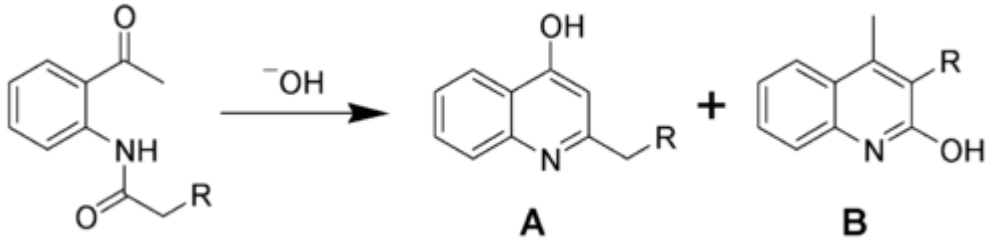


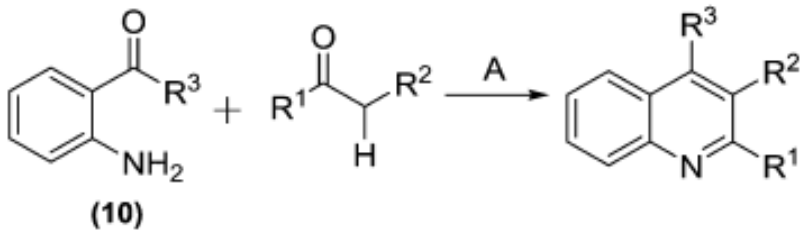
Pfitzinger reaction

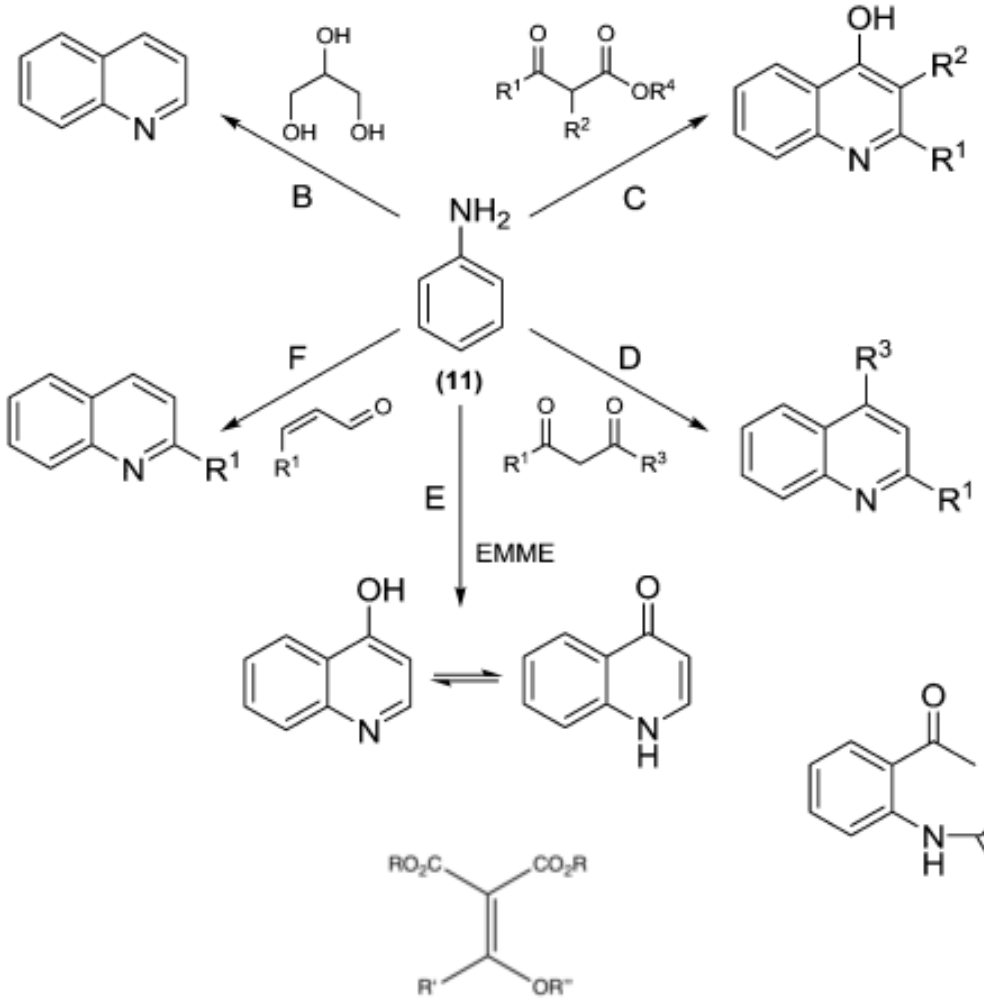


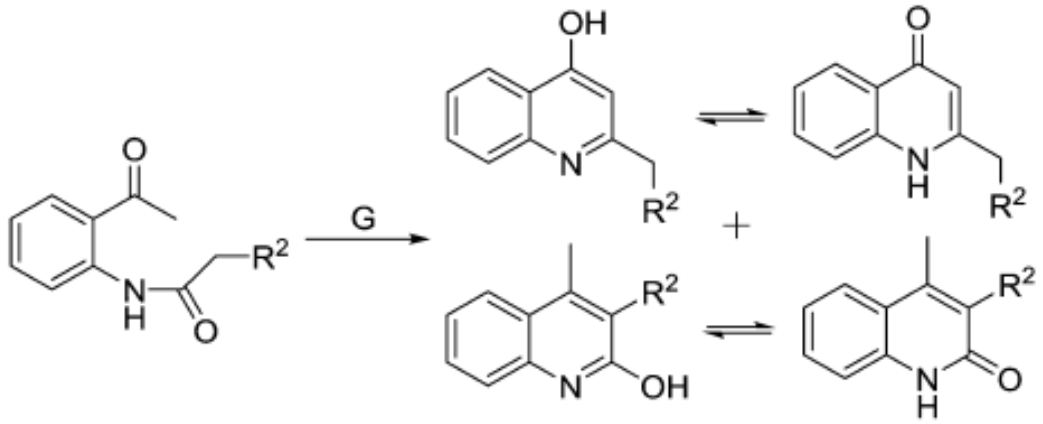


Camps quinoline synthesis









(A) Friedländer
(B) Skraup
(C) Conrad-Limpach
(D) Combes
(E) Gould-Jacobs
(F) Doebner-Miller
(G) Camps

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Thanks