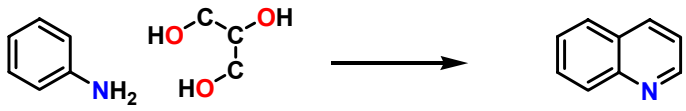
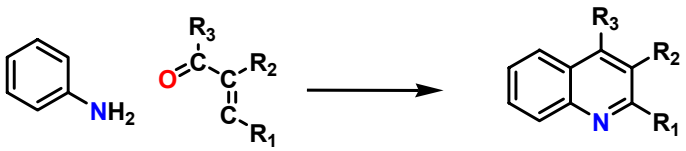
CLASSICAL METHODS OF SYNTHESIZING QUINOLINES

The most obvious starting material for making a quinoline is aniline (aminobenzene) as this and substituted variants can be readily obtained (e.g. via the sequence of nitration and NO_2 reduction).

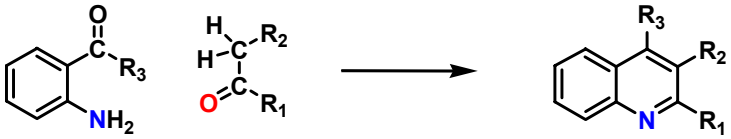
Skraup Synthesis of Quinolines (1880)



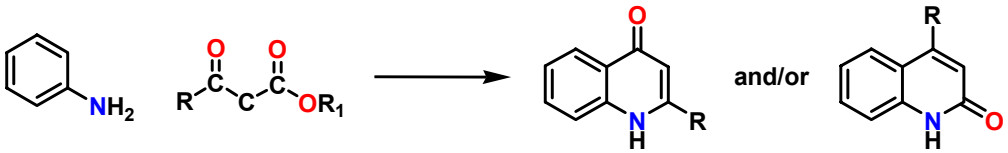
Doebner-von Miller Variation of the Skraup Synthesis (1887)



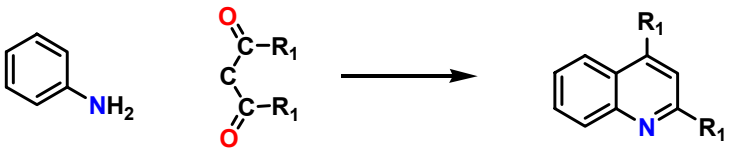
Friedlaender Synthesis of Quinolines (1882)



Conrad-Limpach Synthesis of Quinolones (1887)

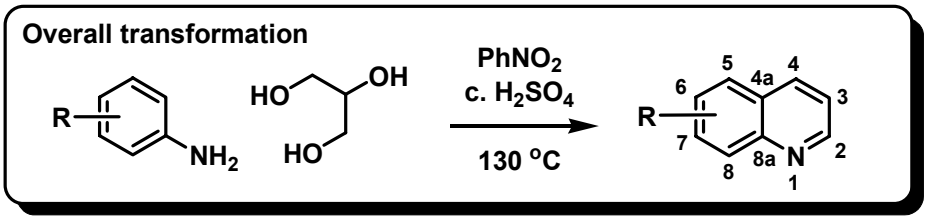


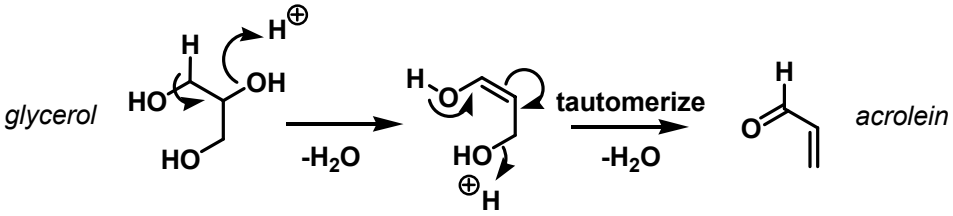
Combes Synthesis of Quinolines (1888)



This reaction will not specifically covered. The mechanism is basically like the first half of the Friedlaender method (imine formation) and second half of the Skraup (acid-catalyzed condensation of the second ketone with the aromatic ring).

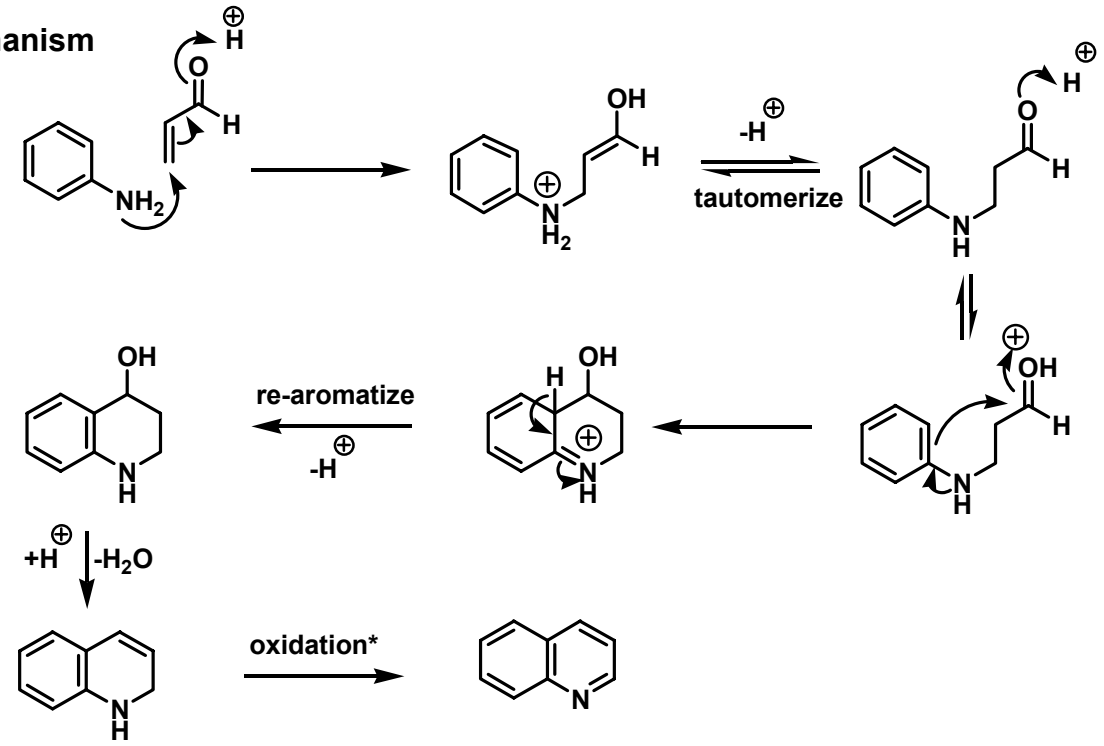
Skraup Synthesis of Quinolines





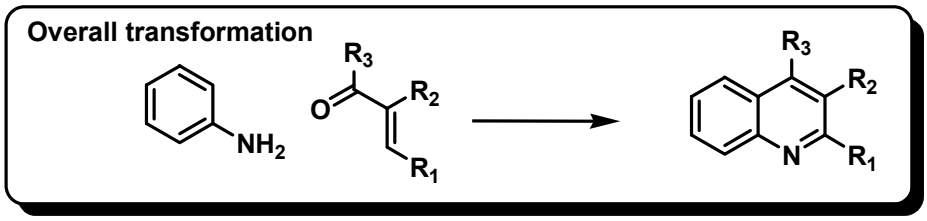
Glycerol is dehydrated in *situ* to give acrolein.

Mechanism

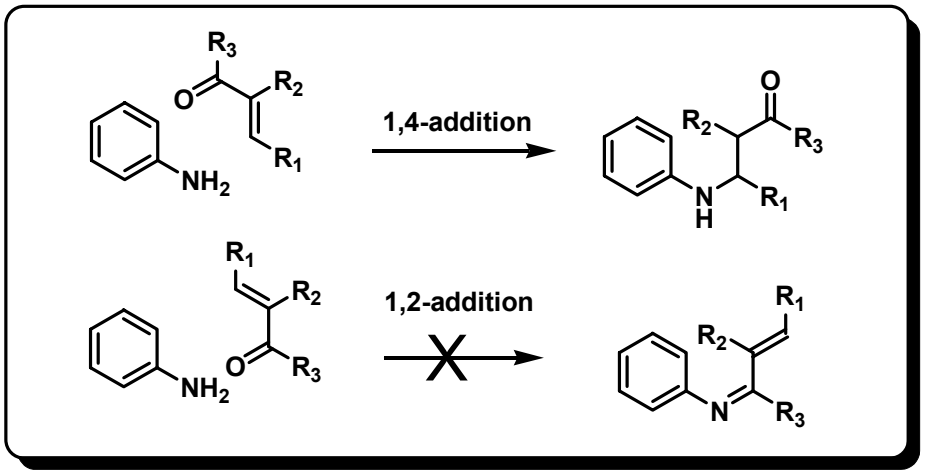


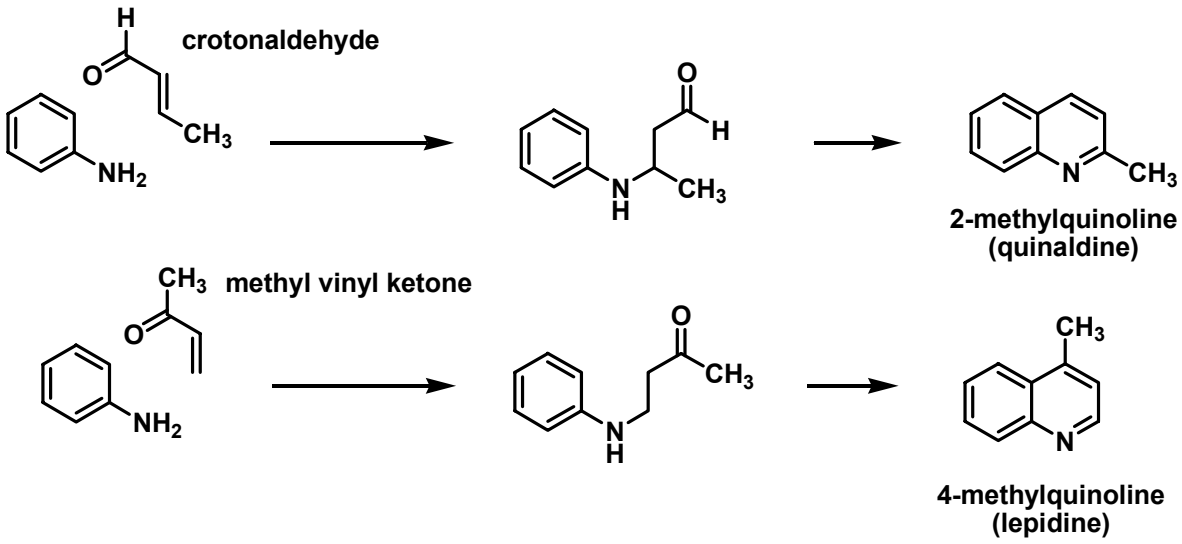
*oxidation can be acheived *in situ* by using nitrobenzene as co-solvent or by using an oxdxant such as iodine or an iron(III) salt.

Doebner-von Miller Variation of the Skraup Reaction



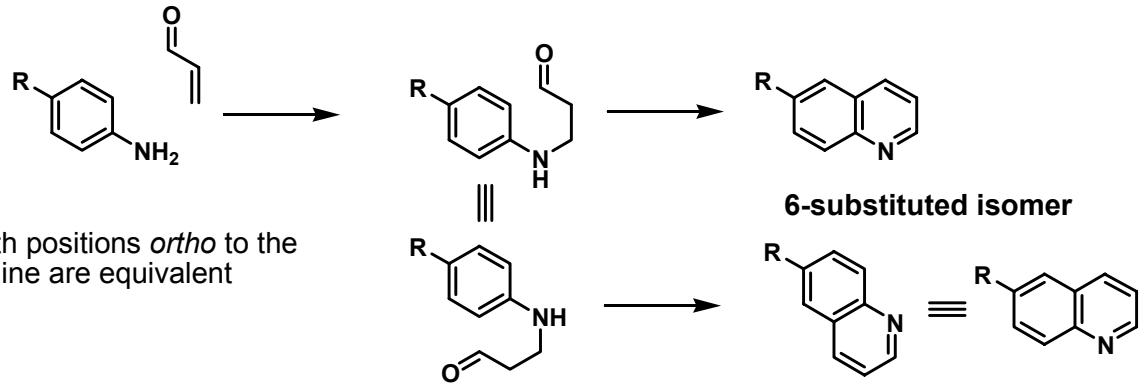
* Uses pre-formed α,β-unsaturated carbonyl compounds instead of acrolein
* Used to provide alkyl and aryl substituents in the "pyridine half" of the quinoline
* The intermediate β-aminocarbonyl compound can be isolated.
* Shows the mechanism starts with a conjugate addition.



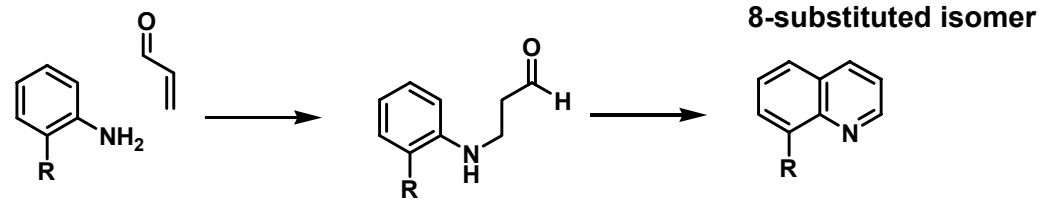


Skraup / Doebner-von Miller Syntheses:
using substituted anilines

***para*-substituted aniline**

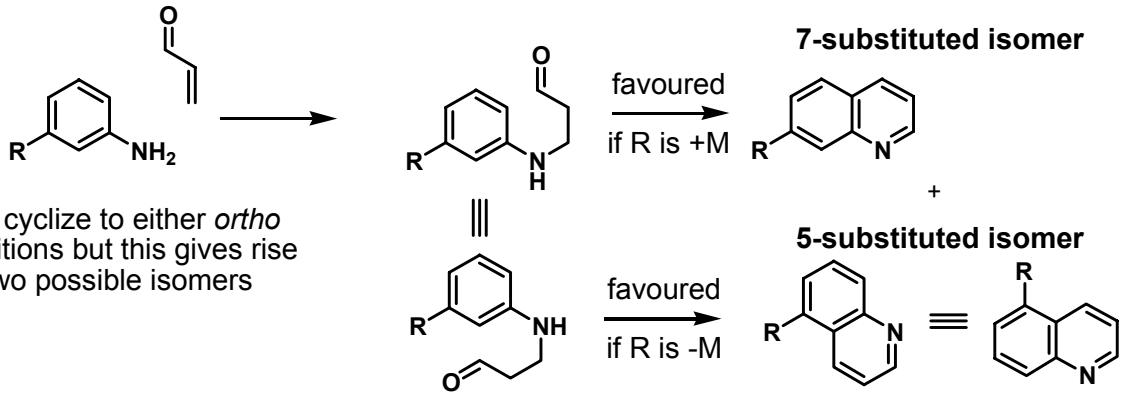


***ortho*-substituted aniline**



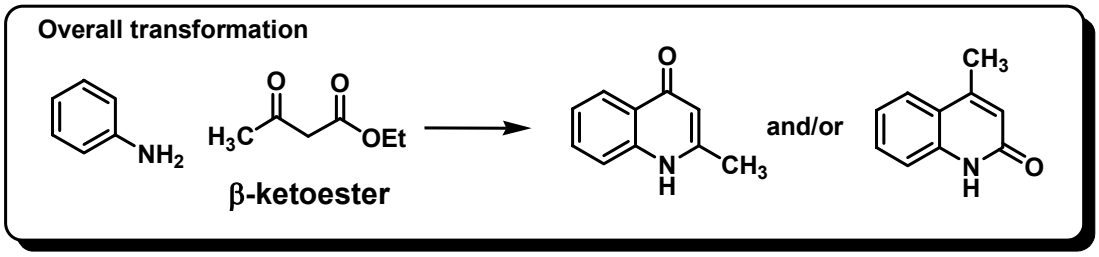
can only cyclize to the unsubstituted *ortho* position

***meta*-substituted aniline** - electronic and steric factors influence cyclization orientation

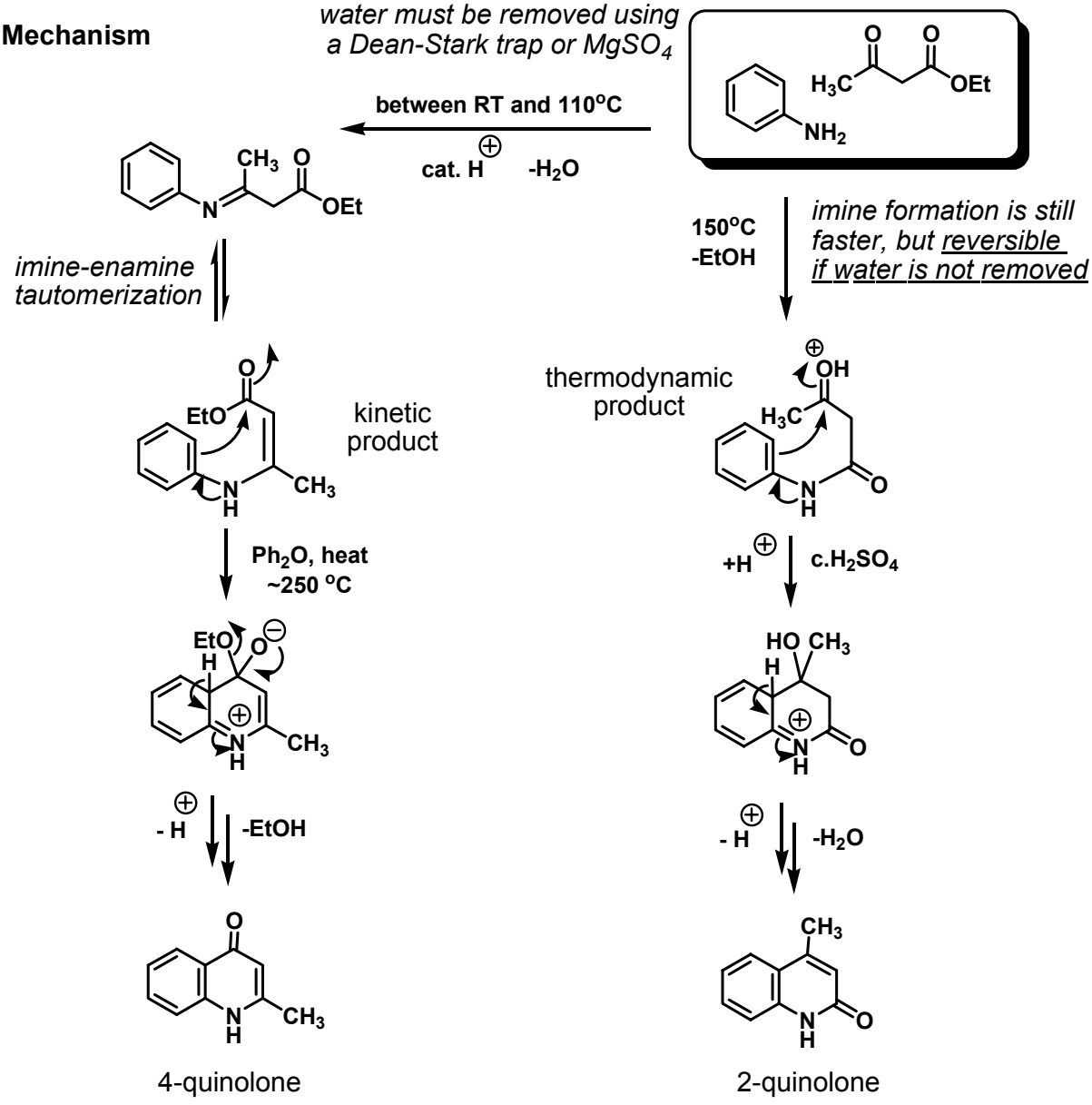


Rate of Reaction: as the ring acts as a nuclophile to attack the protonated aldehyde (see previous slide), an electron withdrawing group R group slows the rate of cyclization whereas an electron donating group increases the rate of cyclization.

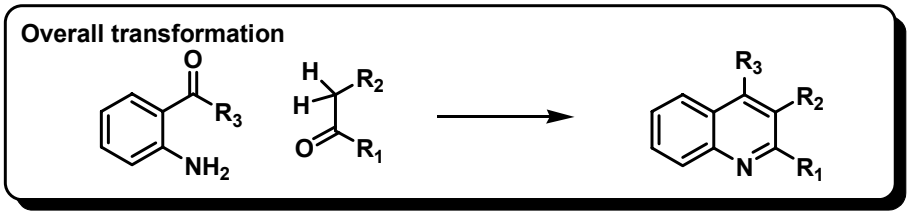
Conrad-Limpach Synthesis of Quinolones



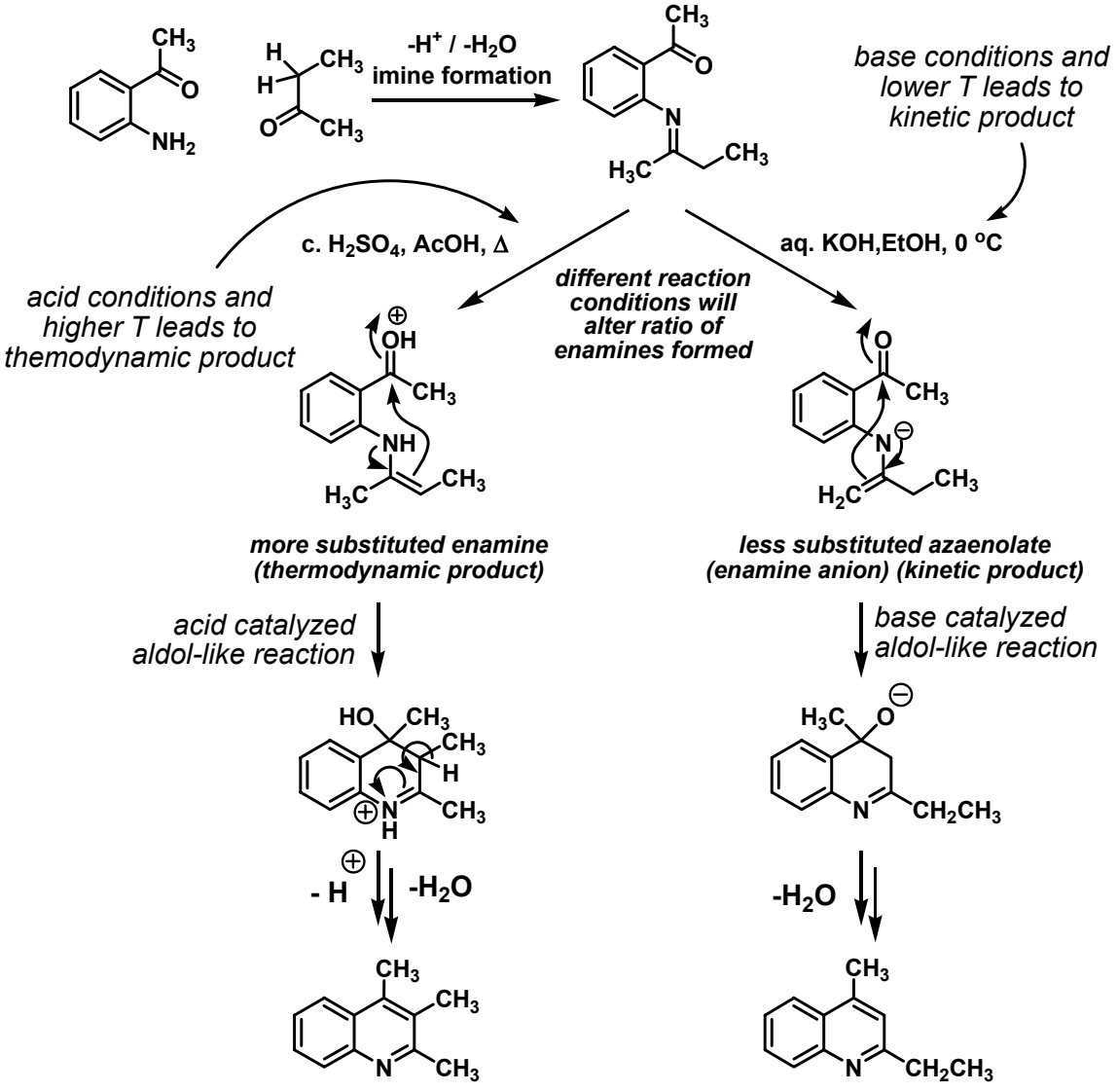
Mechanism



Friedlaender Synthesis of Quinolines



Mechanism - using an unsymmterical dialkyketone as an example



Product distribution is dependent on both reaction conditions and the ketone used (see Fischer indole synthesis for a related discussion). Even different acids (i.e acid strength) can produce different product ratios.