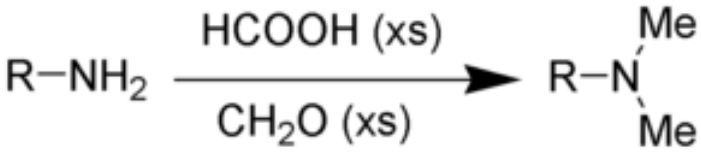
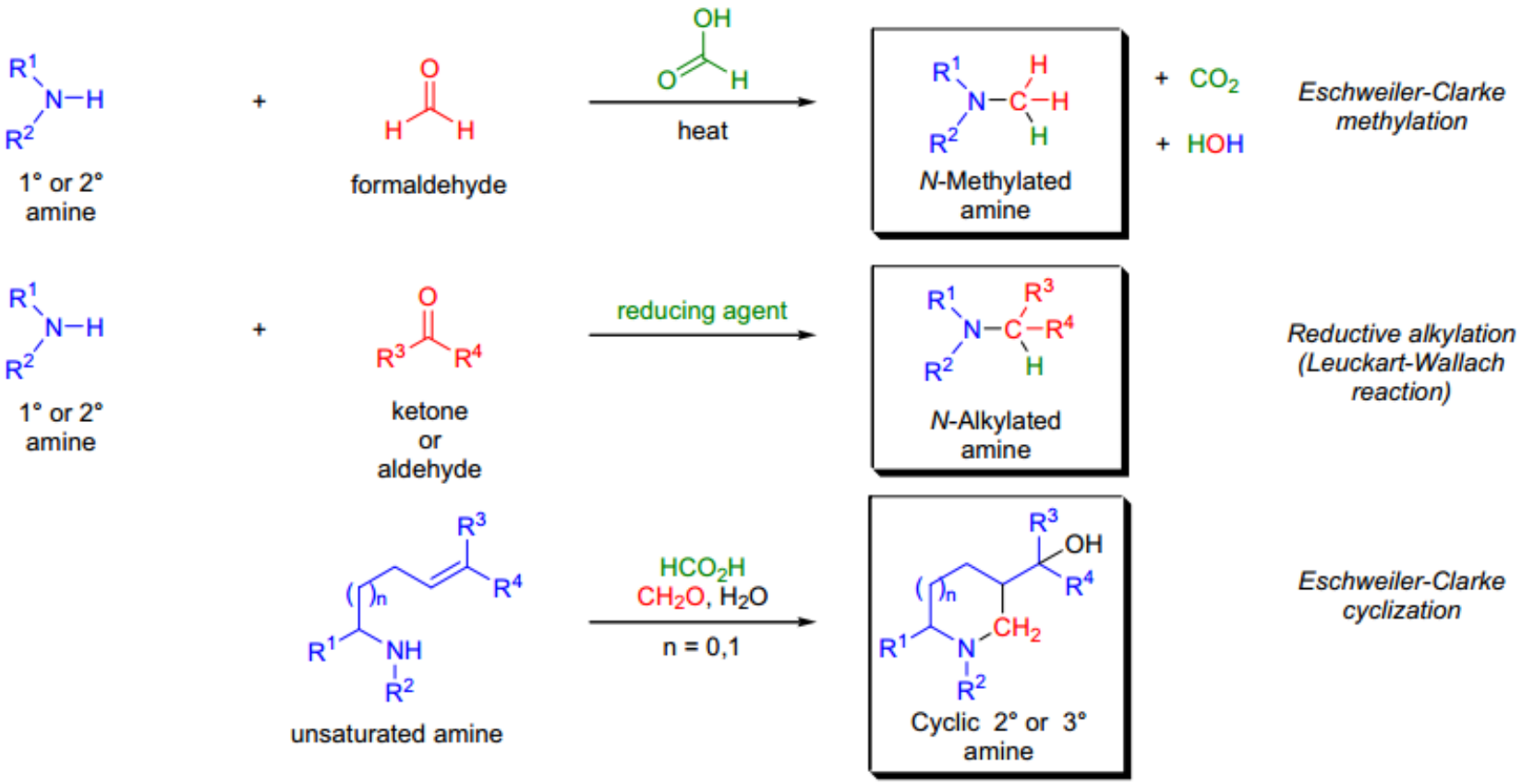
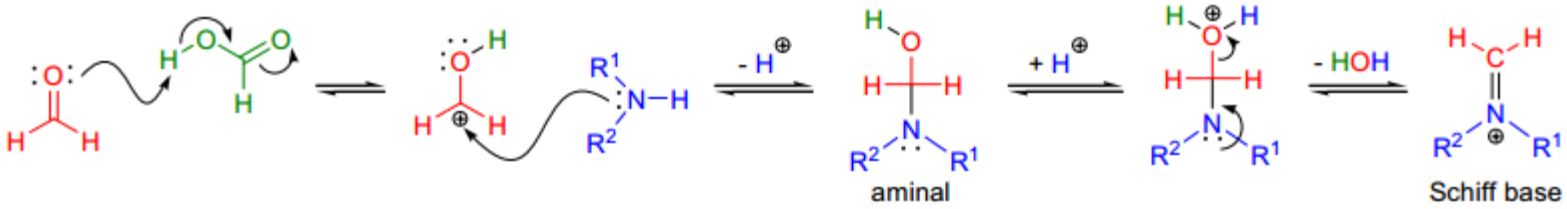
ESCHWEILER-CLARKE METHYLATION

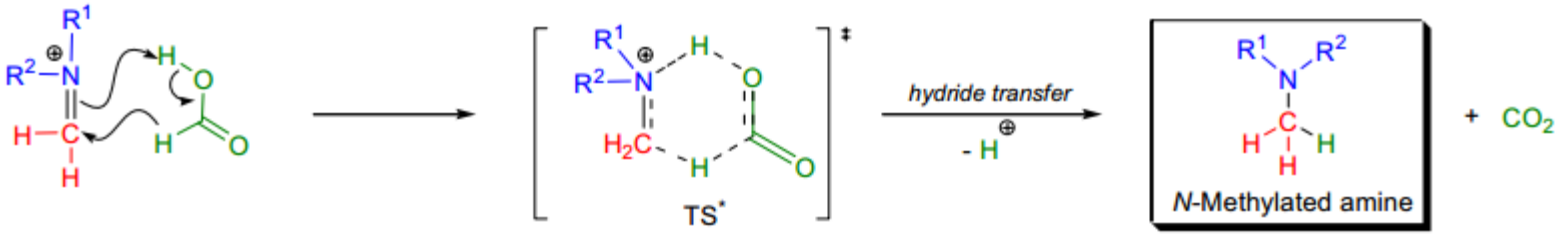


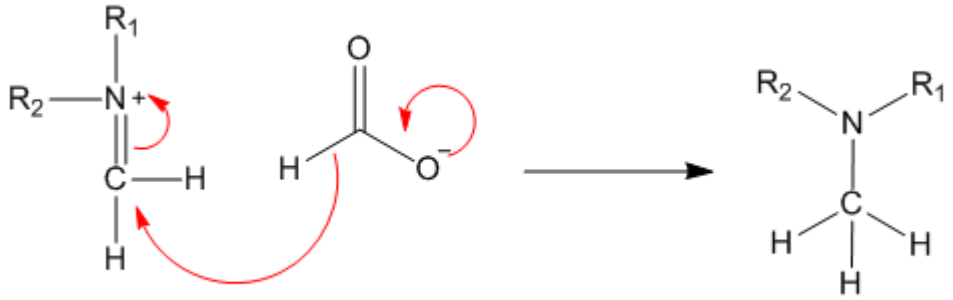


Hydride donor: Formic acid Sodium borohydride, sodium cyanoborohydride, $NaBH_3CN$-$Ti(O\,i\text{-}Pr)_4$, $NaBH(OAc)_3$, borohydride exchange resin (BER)

Mechanism:

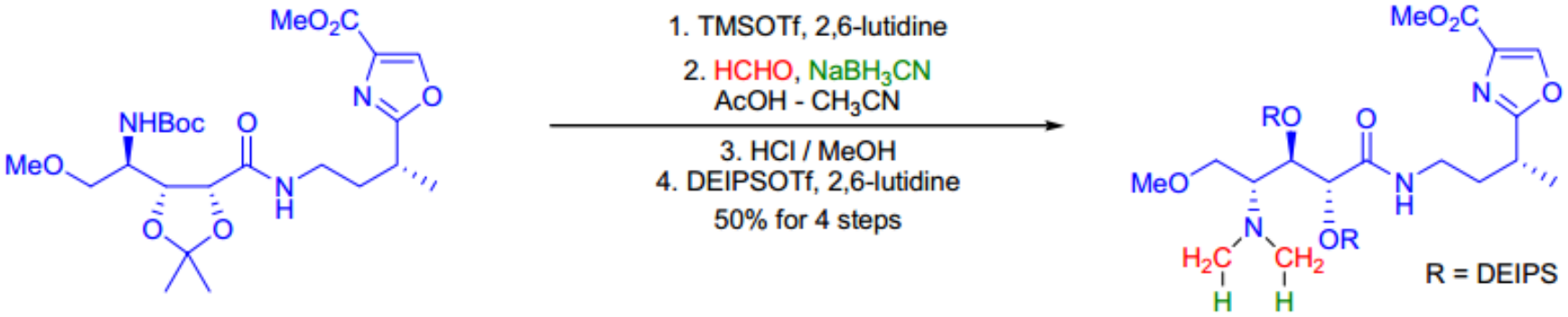

- H⊕
+ H⊕
- HOH
aminal
Schiff base


hydride transfer
- H⊕
TS‡
N-Methylated amine
+ CO2



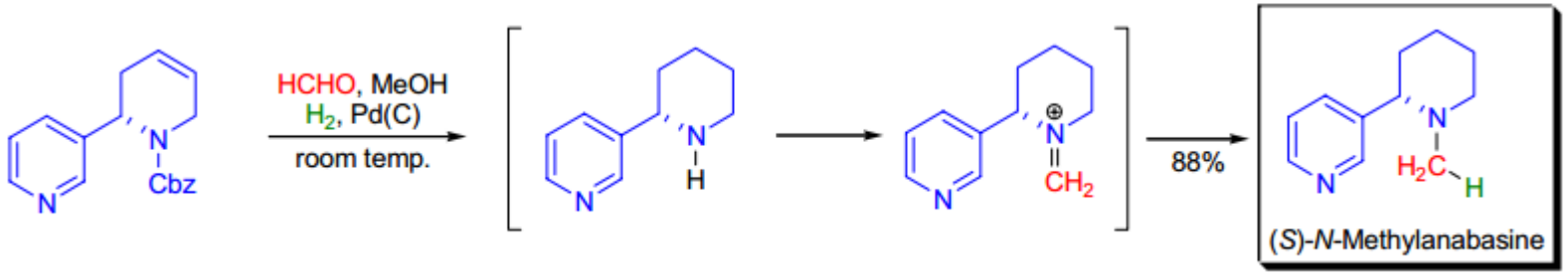
Synthetic Applications

During the total synthesis of (–)-calyculin A and B, A.B. Smith and co-workers utilized a modified *Eschweiler-Clarke methylation* to convert a complex primary amine to the corresponding *N*,*N*-dimethylamino derivative.[27] The *N*-Boc protected primary amine was first deprotected using TMSOTf, followed by introduction of the two methyl groups using $HCHO/NaBH_3CN$ in $AcOH/CH_3CN$ solvent mixture. The acetonide protecting group was subsequently removed, and the resulting diol was silylated.



Synthetic Applications

The enantioselective total syntheses of several piperidine and pyrrolidine alkaloids of tobacco were accomplished in the laboratory of J. Lebreton.[20] In the final stage of the total synthesis of (*S*)-*N*-methylanabasine, a one-pot *Cbz-deprotection-hydrogenation-Eschweiler-Clarke methylation* was carried out using a HCHO/MeOH/Pd(C)/H_2 system at room temperature with an overall 88% yield.



The oxindole alkaloid (–)-horsfiline was synthesized by K. Fuji et al. using an *asymmetric nitroolefination* as the key step.[28] During the endgame of the total synthesis, an *N*-methylation was performed on the five-membered secondary amine using the original *Eschweiler-Clarke methylation* conditions (HCO_2H/HCHO/reflux). Unfortunately, these harsh methylation conditions led to the racemization of the quaternary stereocenter. Therefore, milder modified conditions were applied ($NaBH_3CN$ as the reducing agent) to retain the optical activity of the substrate.