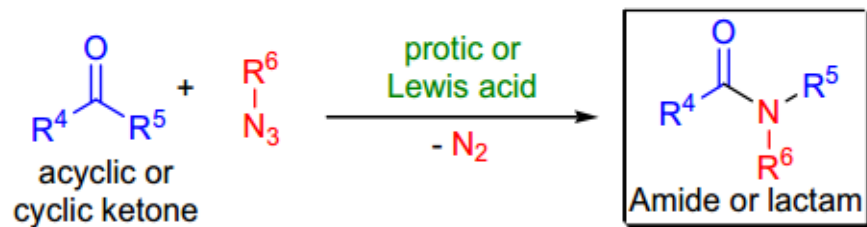
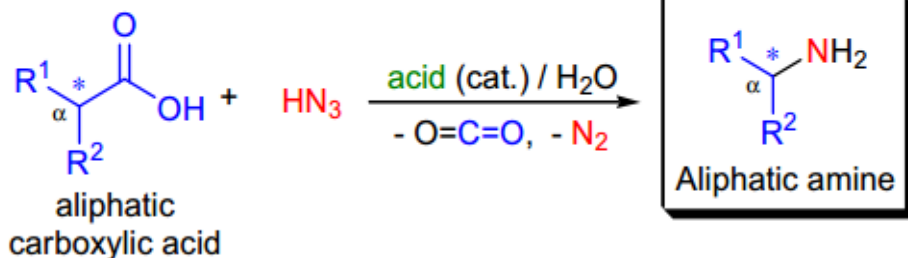
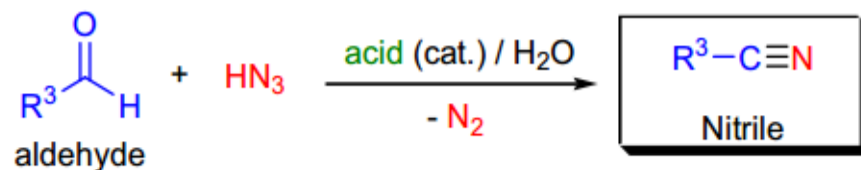
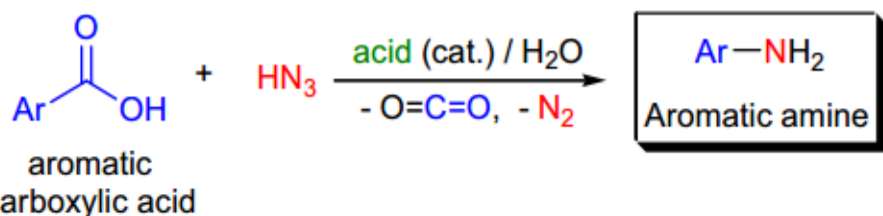
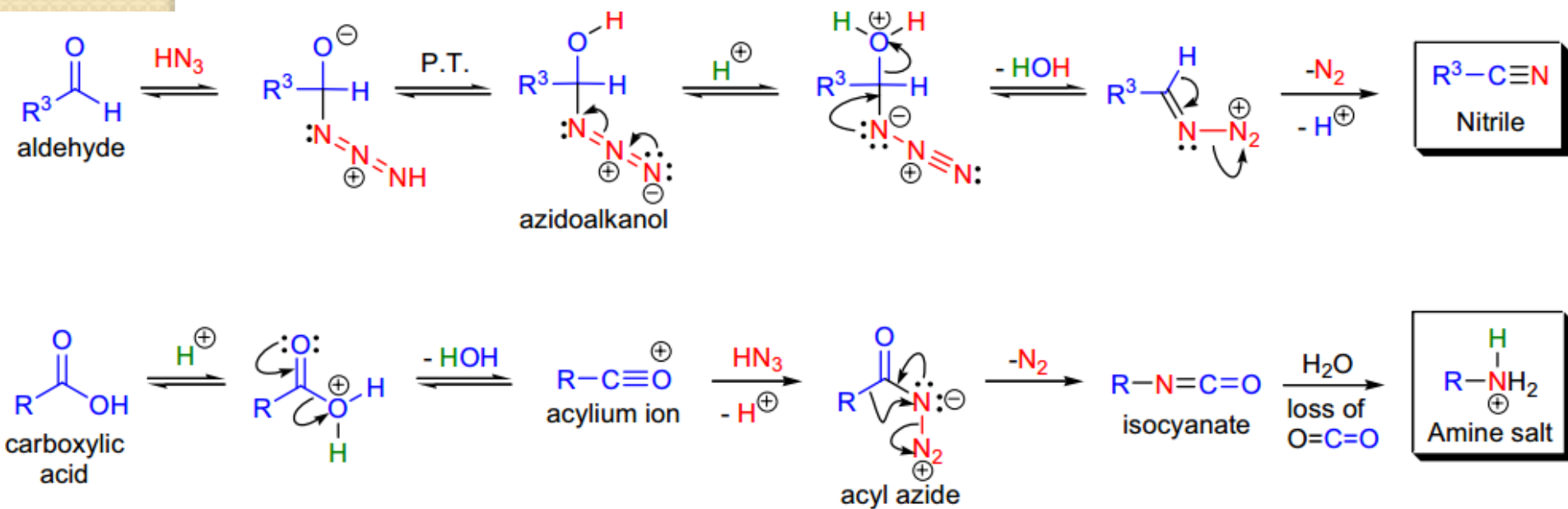


SCHMIDT REACTION



R^{1-2} = alkyl, aryl; Ar = substituted aryl or heteroaromatic; R^3 = Me, substituted aryl; R^4 = alkyl, substituted alkyl; R^5 = aryl;
 R^6 = H, alkyl or aryl; Lewis acid: TiCl_4 , TFA, $\text{CH}_3\text{SO}_3\text{H}$; acid catalyst: H_2SO_4 , PPA, $\text{Cl}_3\text{CCO}_2\text{H}/\text{H}_2\text{SO}_4$, TFA, TFAA

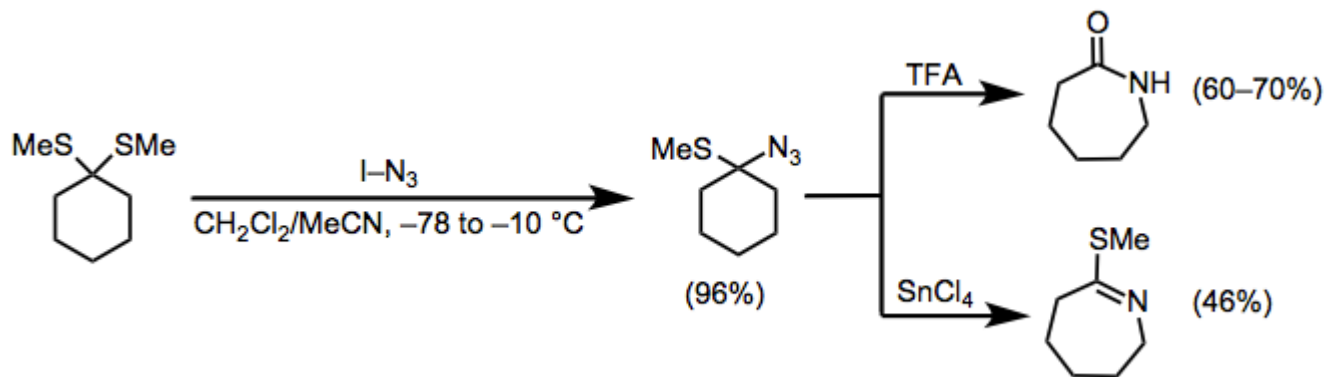
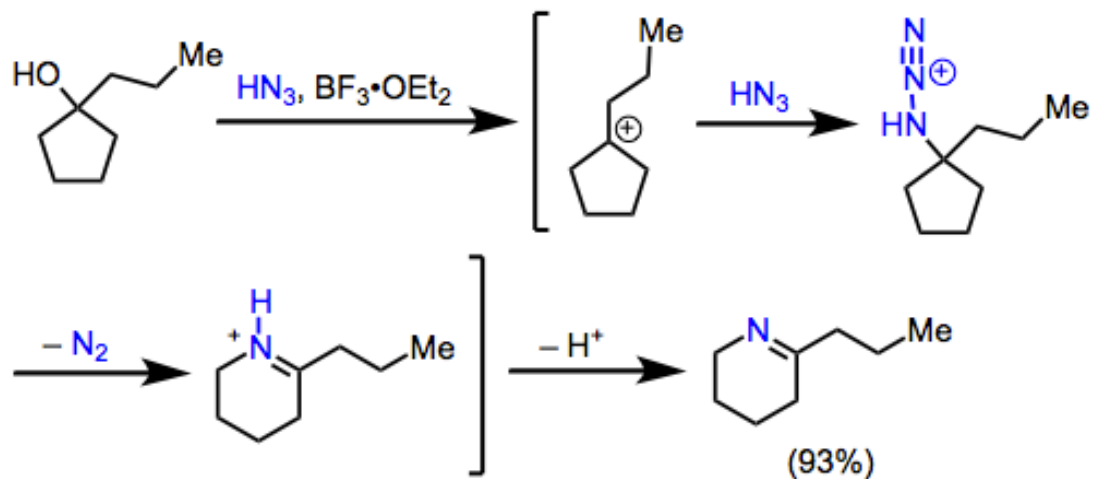
Mechanism



General features

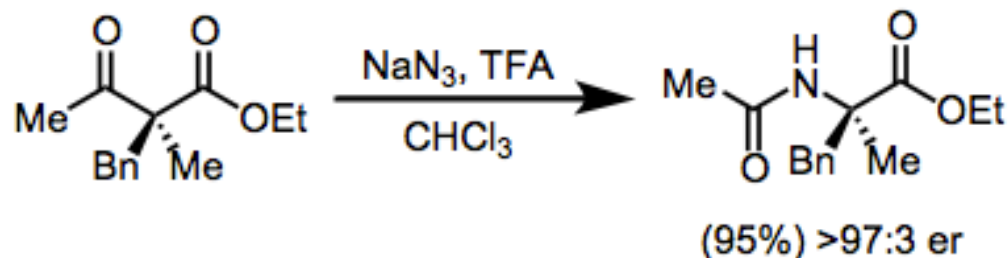
- 1) Hydrogen azide is handled either as a solution in an inert solvent (e.g., CHCl_3) or generated in situ by adding NaN_3 to the acidic reaction mixture; HN_3 is known to be **toxic** and **explosive**.
- 2) The product amines are **one-carbon shorter homologs** of the substrates due to the loss of CO_2
- 3) Aromatic acids with electron-withdrawing groups require the use of very strong acid catalysts (e.g., conc. H_2SO_4 or oleum)
- 4) The α -stereocenter remains unaffected and the product amine is obtained with retention of configuration;
- 5) 1,3-dicarboxylic acids react at **only one** of the carboxylic acid functional groups; α -amino acids do not react.
- 6) Aldehydes and ketones react with hydrazoic acid **faster** than carboxylic acids so good chemoselectivity can be achieved with keto acids;

Reactions of Other Electrophiles

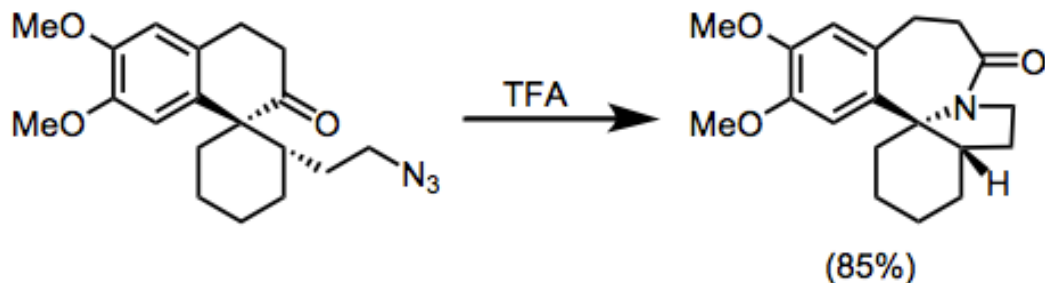


Synthetic Applications

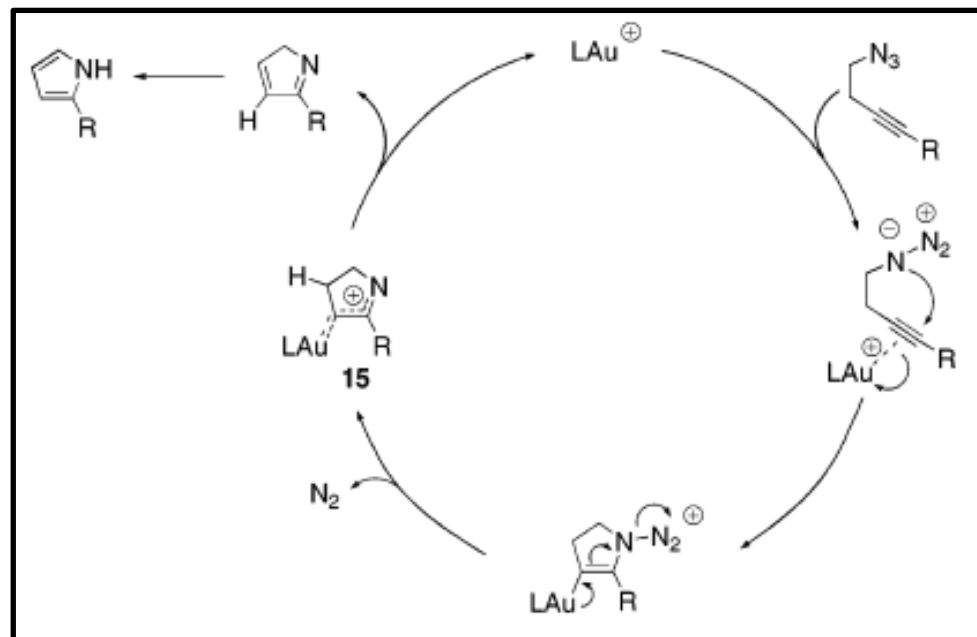
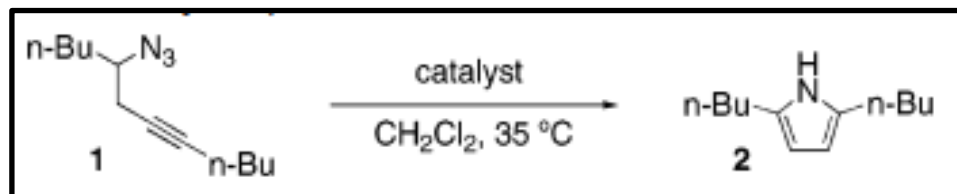
The Schmidt reaction has been applied to the synthesis of disubstituted amino acids. After asymmetric alkylation of a β -ketoester, treatment with trifluoroacetic acid (TFA) and sodium azide yields the N-acetyl amino ester, which may be converted to the corresponding amino acid through functional group manipulations.



The Schmidt reaction has also been applied extensively to access crowded or otherwise difficult amines and amides in alkaloid natural products. Efforts toward the homoerythrina spirocyclic ring system contain a nice application of the intramolecular Schmidt reaction of alkyl azides. An appropriately positioned alkyl azide was smoothly converted to the lactam in the presence of TFA.



Gold(I)-Catalyzed Intramolecular Acetylenic Schmidt Reaction



D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.*, **2005**, *127*, 11260-11261.