STORK ENAMINE SYNTHESIS

History

Vinylamine reactivity known since 1884...

Collie, *Liebigs Ann. Chem.* **1884**, *226*, 294-322
Benary, Ber. *Dtsch. Chem. Ges.* **1909**, *42*, 3912-3925
Robinson, *J. Chem. Soc.* **1916**, *109*, 1038-1046

Wittig coined "enamine" as nitrogen analog of enol in 1927

Wittig, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1085-1094

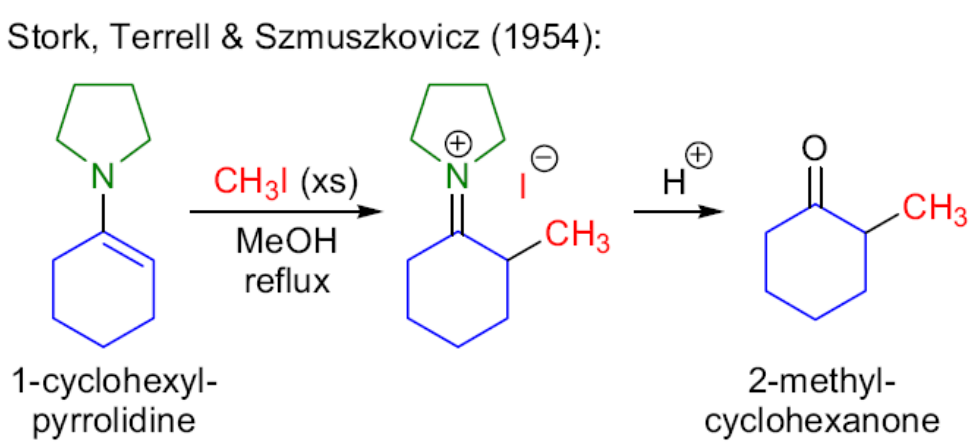
Enamine preparation was first made practical by Mannich in 1936

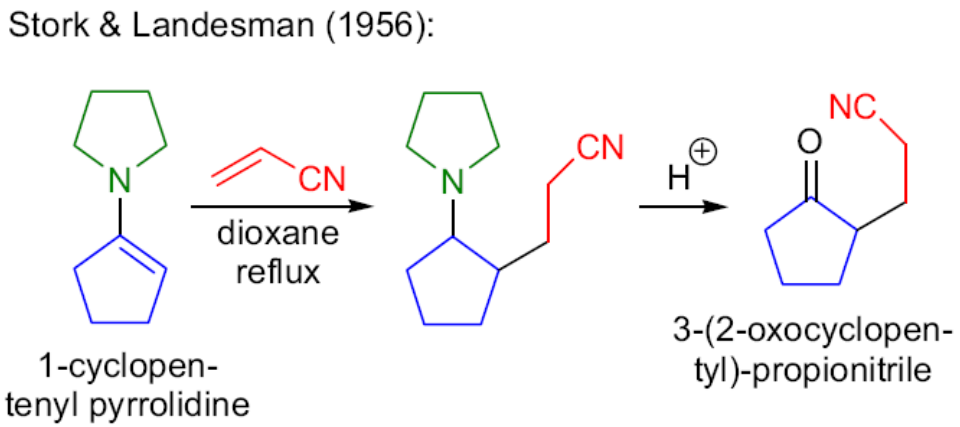
Mannich, *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 2106-2112

But no one seized the opportunity for nearly two decades ! until Stork in 1954

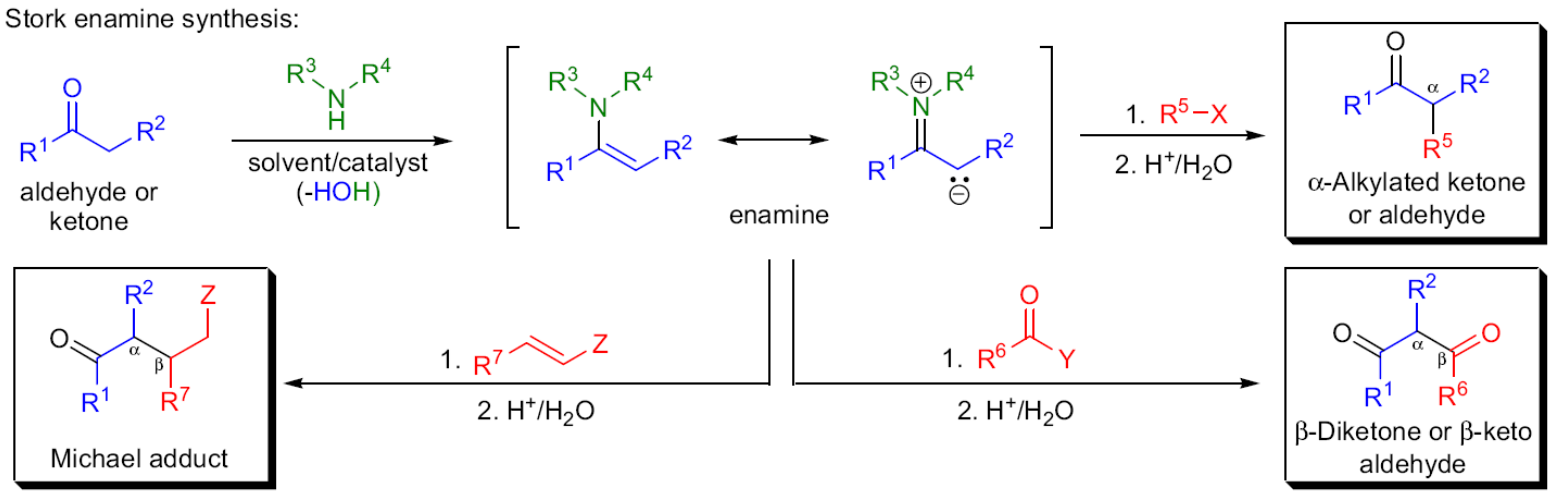
Stork, Terrell, Szmuszkovicz, *J. Am. Chem. Soc.* **1954**, *76*, 2029
Stork, Landesman, *J. Am. Chem. Soc.* **1956**, *78*, 5128
Stork, Landesman, *J. Am. Chem. Soc.* **1956**, *78*, 5129
Stork, Brizzolara, Landesman, Szmuszkovicz, Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207

In 1954, G. Stork and co-workers discovered that the reaction of enamines with alkyl- or acyl halides followed by acidic hydrolysis constituted a novel way for the α-alkylation or α-acylation of carbonyl compounds



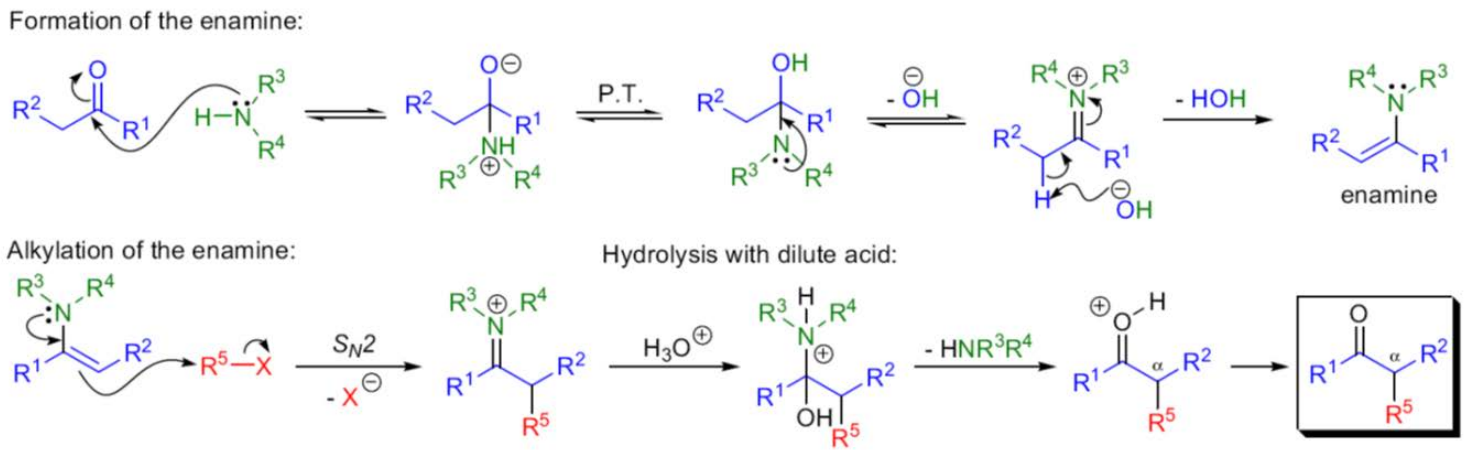


The synthesis of α-alkyl- or acyl carbonyl compounds via the alkylation or acylation of the corresponding enamines is known as the ***Stork enamine synthesis***.



R^1 = H, alkyl, substituted alkyl; R^2 = H, alkyl, aryl; $R^{3\text{-}4}$ = alkyl, aryl; R^5 = 1° or 2° alkyl, allylic, benzyl, CH_2CO_2R, CH_2CN, propargylic; R^6 = alkyl, aryl, OR, H; R^7 = H, alkyl, aryl; X = Cl, Br, I, OTs; Y =OCOR, CN, Cl, Br, I; Z = CN, COR, CO_2R, NO_2

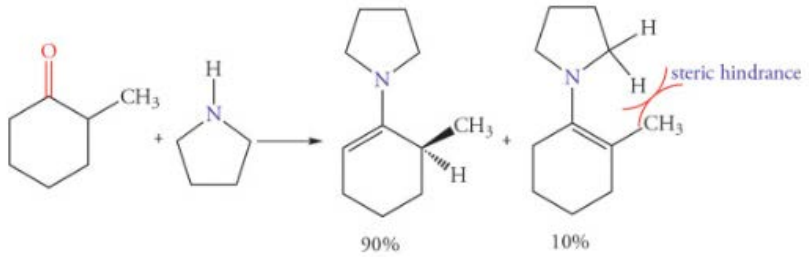
Mechanism: [24,25]



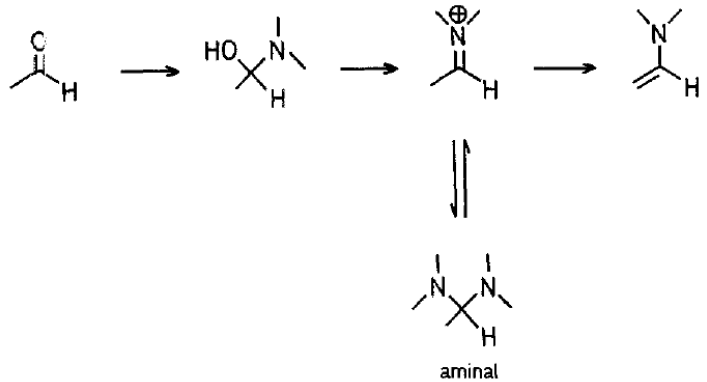
The general features of this method are:

1) The enamines are prepared by reacting the aldehyde or ketone with one equivalent of secondary amine (e.g., piperidine, morpholine or pyrrolidine) in the presence of a catalyst (or dehydrating agent)

2) With unsymmetrical ketones the formation of enamine regioisomers is expected but usually the less substituted regioisomer is favored(1,3-allylic strain)



3) The preparation of aldehyde enamines is often accompanied by the formation of aminals, which can be converted to the desired enamines by destructive distillation

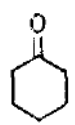
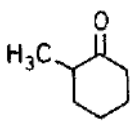
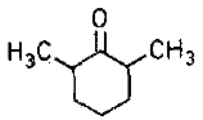
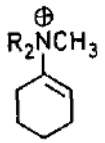
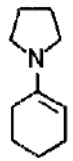
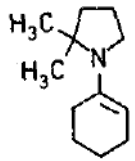


4) Activated alkyl and acyl halides are the best reaction partners (e.g., allyl-, benzyl-, propargylic-, or activated aryl halides)

5) Tertiary alkyl halides do not alkylate the enamines but rather undergo elimination

6) Other electrophiles such as Michael acceptors and epoxides can also be used

7) The bulkier the ketone and the amine components, the better the yields of the monoalkylated product, but the reaction rates tend to drop.

	Products and Distribution			
				
	16	37	16	31
	18	60	9	13

Advantages of the Stork enamine synthesis are:

1) The alkylation of the enamine takes place under neutral conditions, which is important when the substrate is base or acid sensitive;

2) Polyalkylated products are seldom observed

3) The alkylation takes place on the less substituted side of the ketone

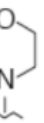
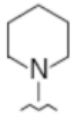
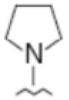
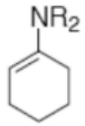
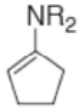
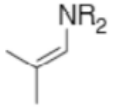
4) An asymmetric version utilizing chiral enamines is also available.

Structure – Nucleophilicity Relationships for Enamines

Bernhard Kempf, Nathalie Hampel, Armin R. Ofial, and Herbert Mayr*[a]

Dedicated to Professor Richard Kreher on the occasion of his 70th birthday

Table 5. Comparison of relative rate constants k_{rel} for the reactions of enamines with various electrophiles.

Reactions		Relative reactivities k_{rel} of enamines		
	NR_2 =			
	+ $(lil)_2CH^+$ (CH_2Cl_2, 20 °C)	1	32	937
	+ $(jul)_2CH^+$ (CH_2Cl_2, 20 °C)	1	42	1370
	+ $(lil)_2CH^+$ (CH_2Cl_2, 20 °C)	1	24	268
	+ $(jul)_2CH^+$ (CH_2Cl_2, 20 °C)	1	26	189
	+ $(thq)_2CH^+$ (CH_2Cl_2, 20 °C)	1	26	262
	+ PhN_3 (C_6H_6, 25 °C)[a]	1	–	45
	+ PhN_3 ($CHCl_3$, 44.8 °C)[b]	1	5	155
	+ $Ph_2C{=}C{=}O$ (PhCN, 40.3 °C)[c]	1	–	1420
	+ H_3O^+ (H_2O, 25 °C)[d]	1	452	27100

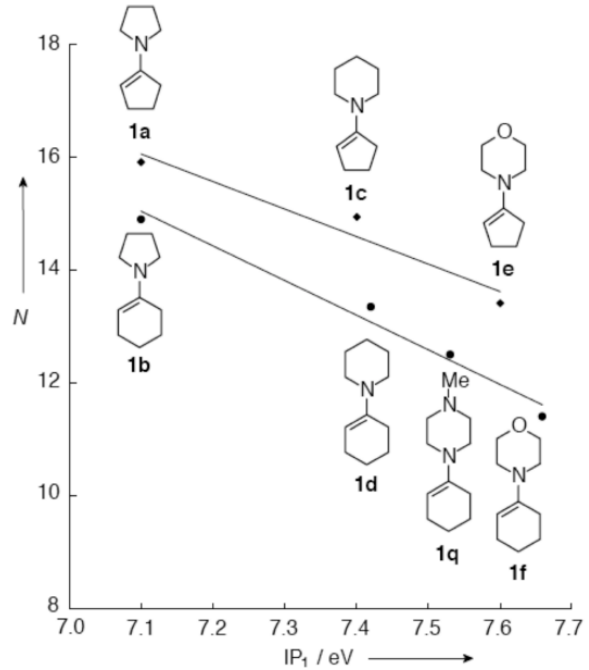
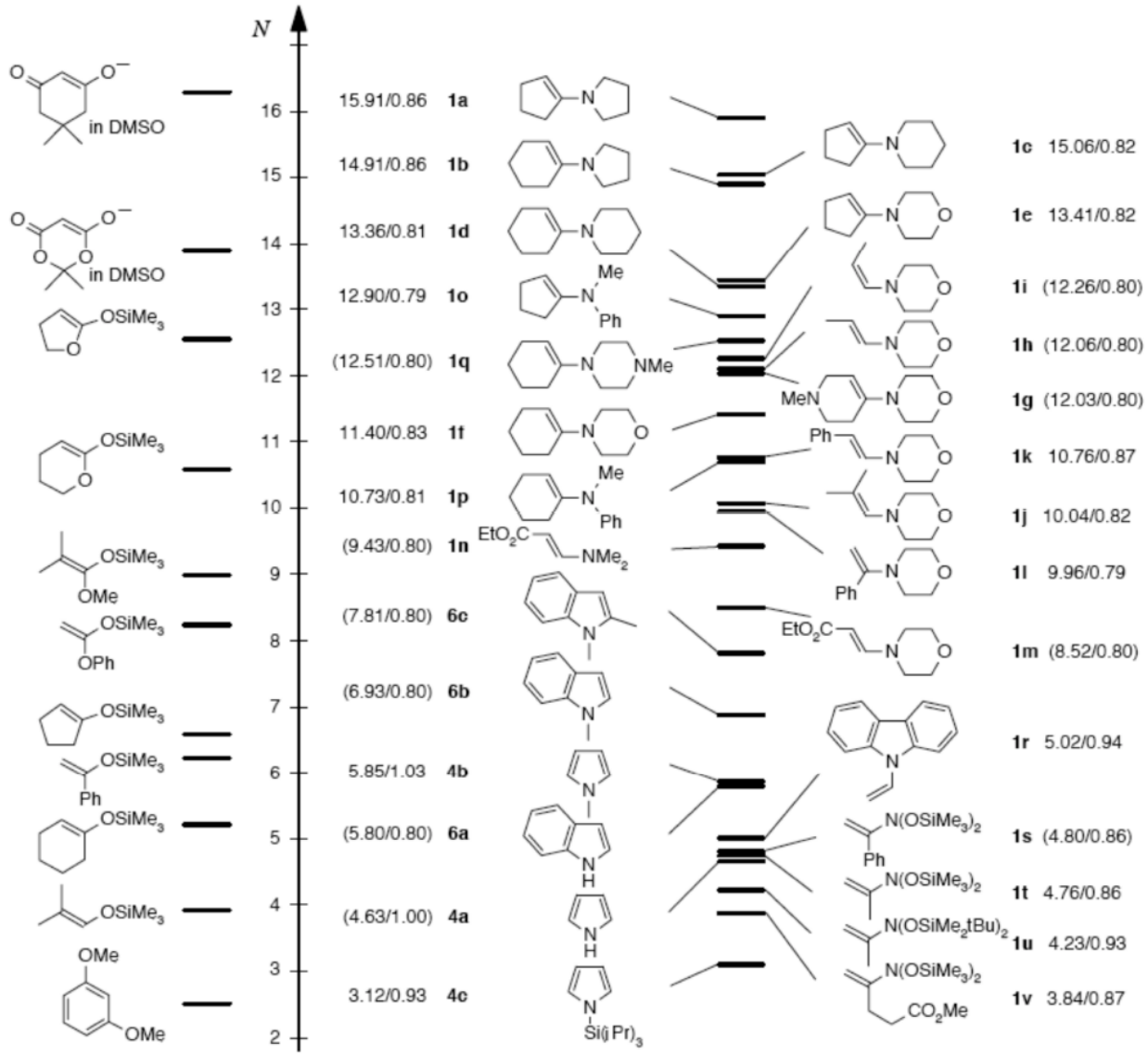


Figure 5. Correlation of the nucleophilic reactivities N with the first vertical ionization potentials IP_1 for cyclic enamines[41] (cyclopentenes: $N = -4.86\,IP_1 + 50.54$, $n = 3$, $r^2 = 0.9397$; cyclohexenes: $N = -6.11\,IP_1 + 58.44$, $n = 4$, $r^2 = 0.9772$).

consequently reduces nucleophilicity. The increasing degree of pyramidalization of nitrogen from pyrrolidino to piperidino and morpholino has also been confirmed by X-ray crystallography of derivatives of these compounds.[42]



As shown in Figure 9, enamines cover a wide range of nucleophilicity from $N \approx 4$ such as typical enol ethers[17] to $N \approx 16$ such as stabilized carbanions in DMSO.[21] For a typical s value of 0.85, this range corresponds to roughly ten orders of magnitude in rate constants or relative reaction times of one minute for **1a** versus 20000 years for **1v**. The benefit of this scale in synthesis design is obvious.

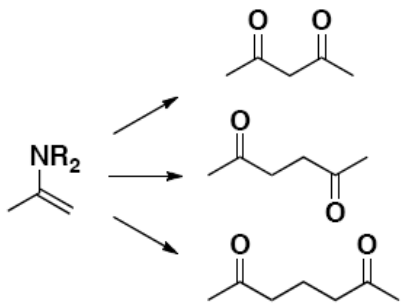
$$\log k\,(20\,^{\circ}\mathrm{C}) = s(N+E)$$

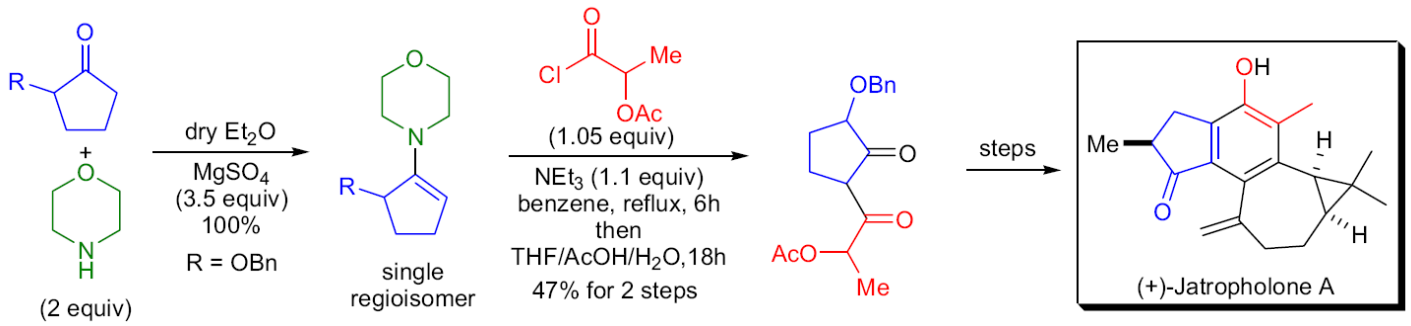
Representative <u>Sampling</u> of Synthetic Uses:

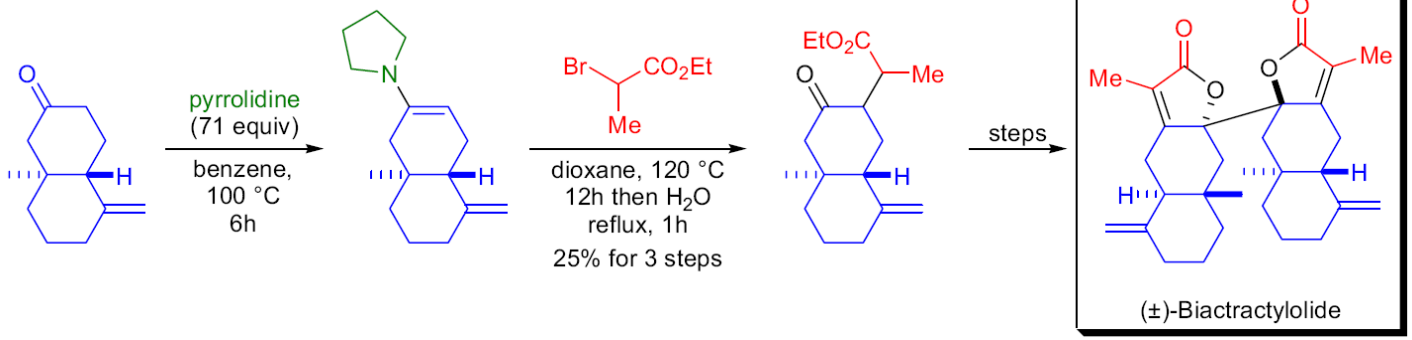
Generating 1,3-dicarbonyl: Acylation

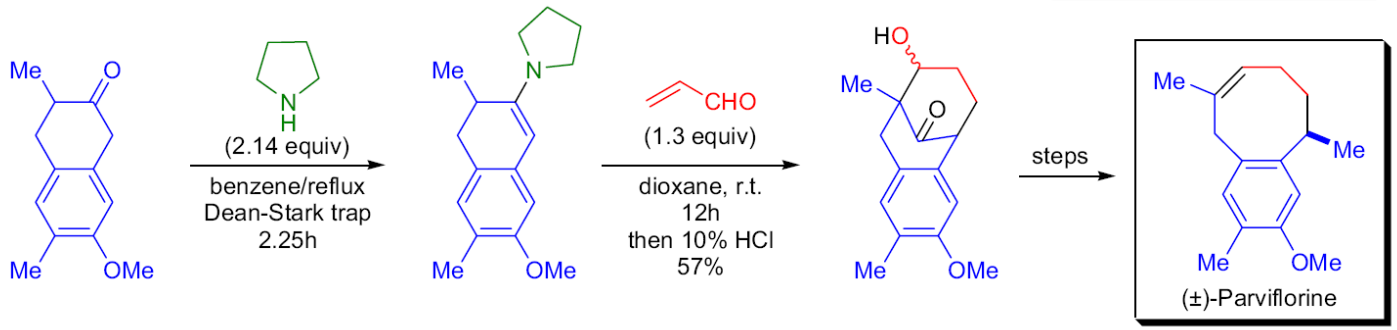
Generating 1,4-dicarbonyl: Alkylation

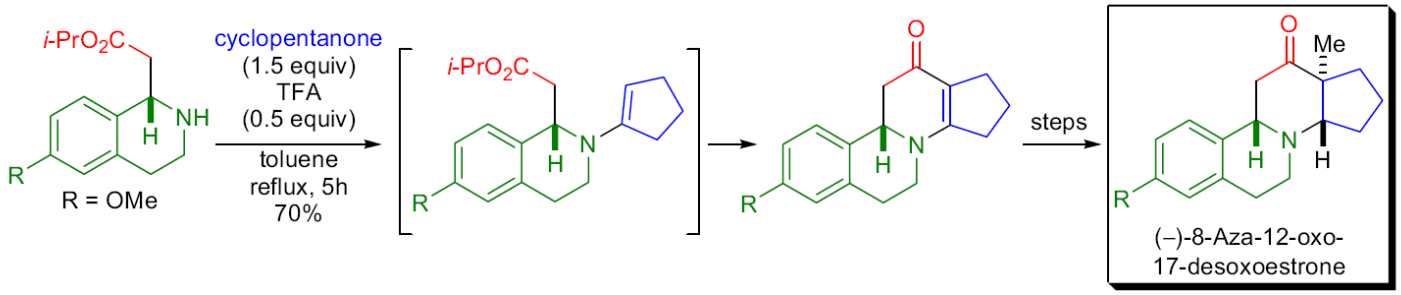
Generating 1,5-dicarbonyl: Michael Addition



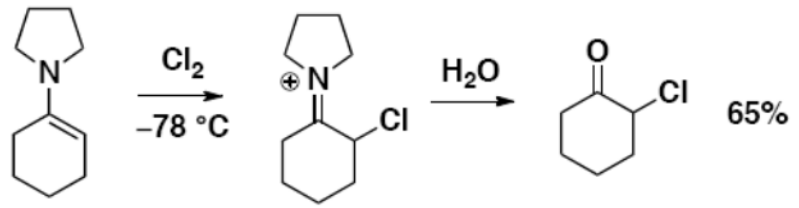




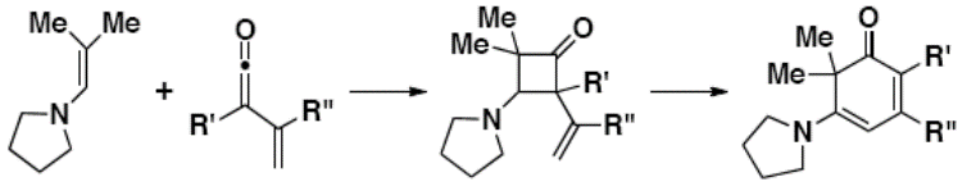




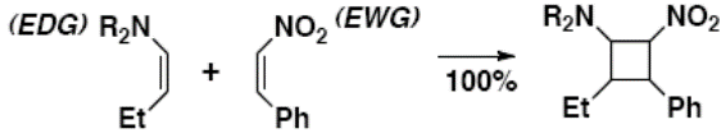
Halogenation:
α–chlorination (*Chem. Ber.* **1979** 1670)



Cycloadditions:
[2+2] with vinylketenes (*HCA* **1982** 2230)

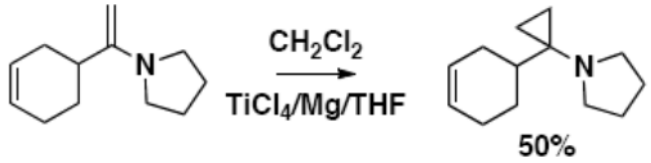


[2+2] with nitrostyrenes (*JOC* **1965** 4280)



[4+2] with pyrones (*JOC* **1983** 4869)

Cyclopropanation:
(*Org. Lett.* **2006** 2261



Michael-Stork addition:
(Silvestri, *JOC* **2005** 8239)