

ROBINSON ANNULATION

(References are on page 665)

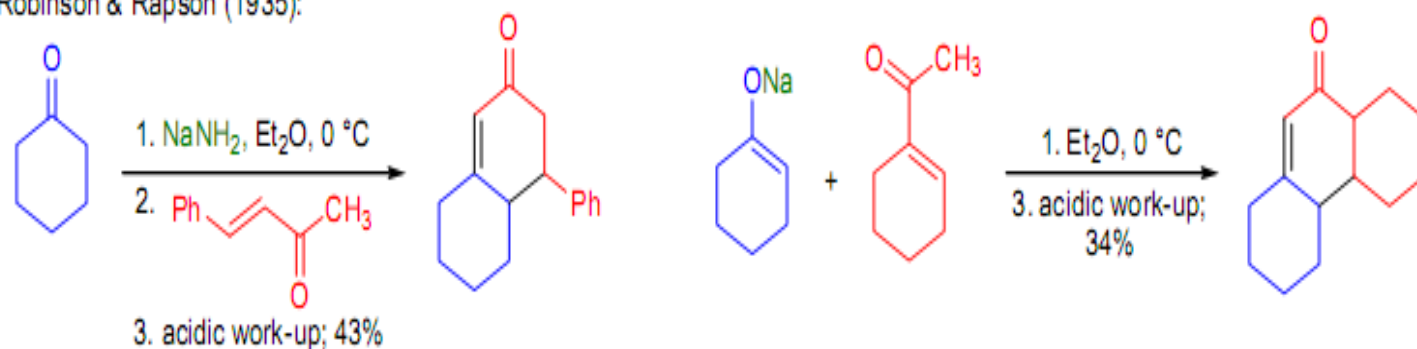
Importance:

[*Seminal Publications*^{1,2}; *Reviews*³⁻⁹; *Modifications & Improvements*¹⁰⁻³⁶]

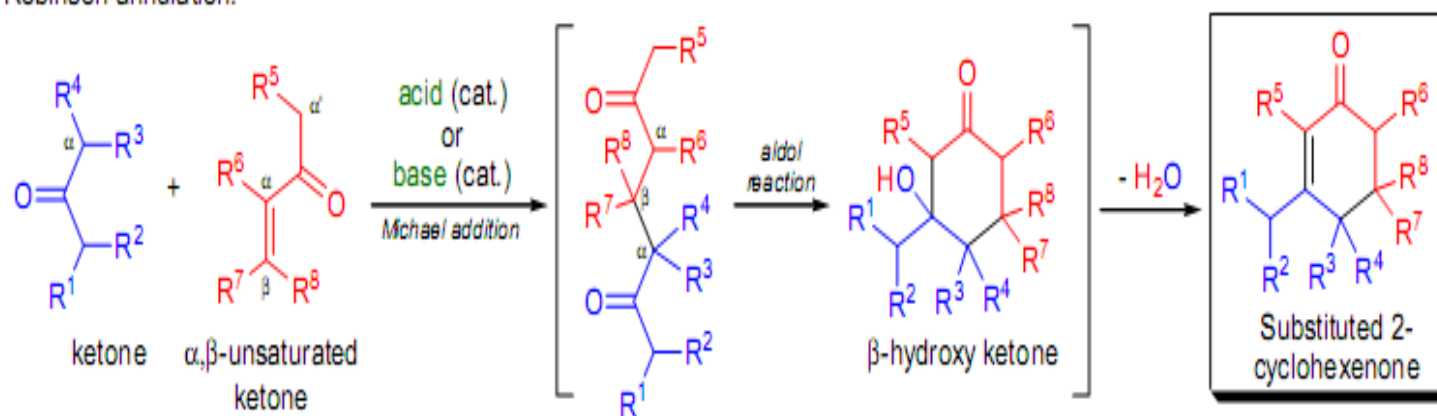
In 1935, R. Robinson and W.S. Rapson were preparing substances related to the sterols when they found that the sodium enolate of cyclohexanone reacted with various acyclic and cyclic α,β -unsaturated ketones to afford substituted cyclohexenones.¹ Robinson recognized the generality of this transformation, which was quickly adapted by the synthetic community, and today it is widely used in the synthesis of complex natural products. The reaction of a ketone (most often a cyclic one) with an α,β -unsaturated ketone to give a substituted cyclohexenone derivative is known as the *Robinson annulation*. The general features of the reaction are: 1) it is a combination of three reactions: *Michael addition*, *intramolecular aldol reaction*, and dehydration; 2) it can be both acid- and base-catalyzed, but predominantly the reaction is conducted under basic conditions; 3) acyclic enones and cyclic ketones afford bicyclic enones, whereas cyclic enones and cyclic ketones give rise to polycyclic fused enones; 4) methyl vinyl ketone (MVK) and its various derivatives and surrogates are used most often as the enone component; 5) can be conducted as a one-pot process, but yields tend to be higher when the Michael adduct is isolated and then subjected to the *aldol reaction*; 6) the alkylation of an unsymmetrical ketone occurs regioselectively at the most substituted α -position unless severe steric interference dictates otherwise; 7) regioselective cyclization can also be achieved by using pre-formed enolates or enamines under non-equilibrium conditions; 8) the annulation can generate as many as five stereocenters, but in the dehydration step two of these chiral centers are lost; 9) the relative stereochemistry between R^3 and R^7 (*cis* or *trans*) is dependent on the reaction conditions (e.g., solvent);¹¹ and 10) the enantioselective version is known as the *Hajos-Parrish reaction*.^{10,13}

Robinson & Rapson (1935):

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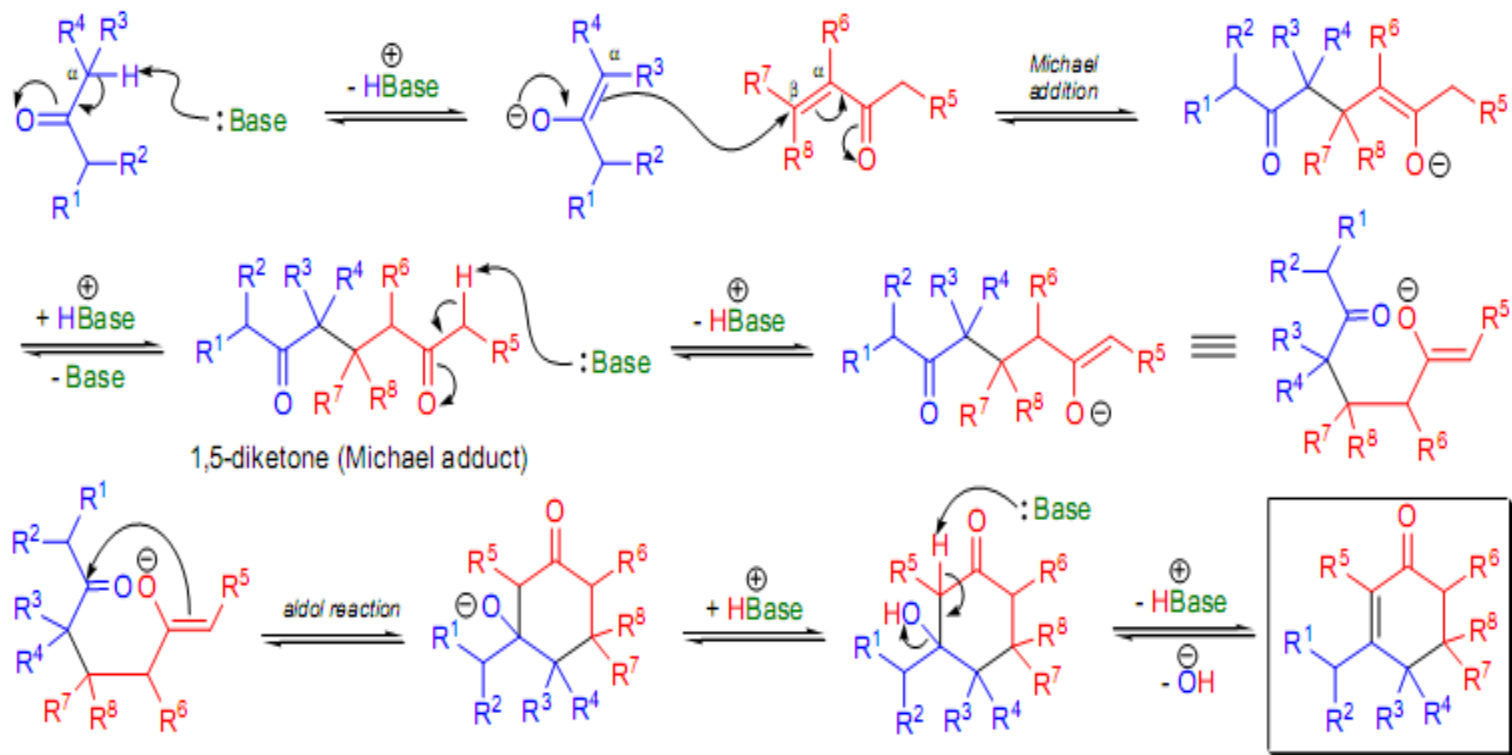
Robinson annulation:



R^{1-4} = H, alkyl, aryl; R^5 = H, alkyl, aryl; R^6 = H, alkyl, aryl, SiR_3 ; R^{7-8} = H, alkyl, aryl

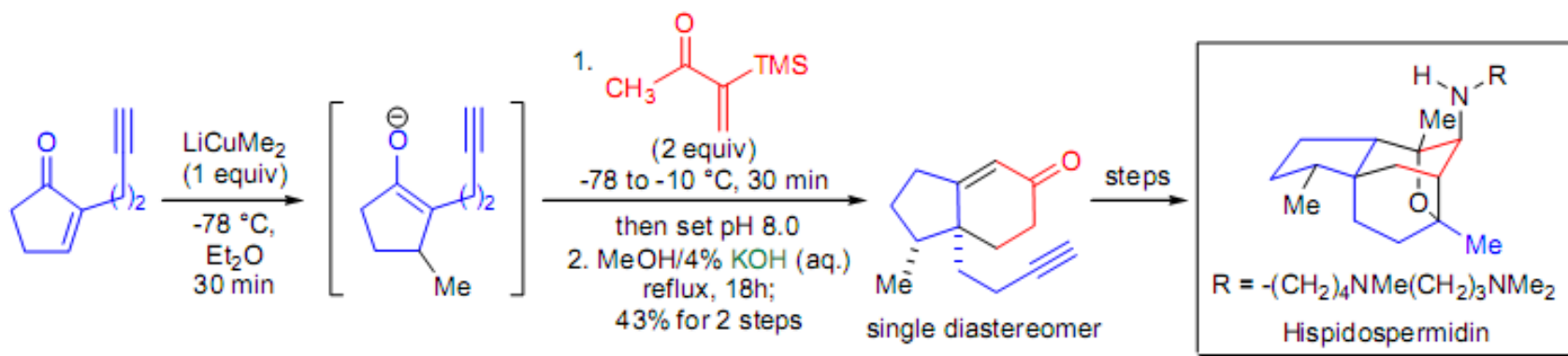
Mechanism: ^{11,15,4}

The *Robinson annulation* has three distinct steps: the *Michael addition* of the enol or enolate across the double bond of the α,β -unsaturated ketone to produce a 1,5-diketone (Michael adduct), followed by an *intramolecular aldol reaction*, which affords a cyclic β -hydroxy ketone (keto alcohol), and finally a base-catalyzed dehydration which gives rise to the substituted cyclohexenone. An alternative mechanism *via* disrotatory electrocyclic ring closure is possible.¹¹

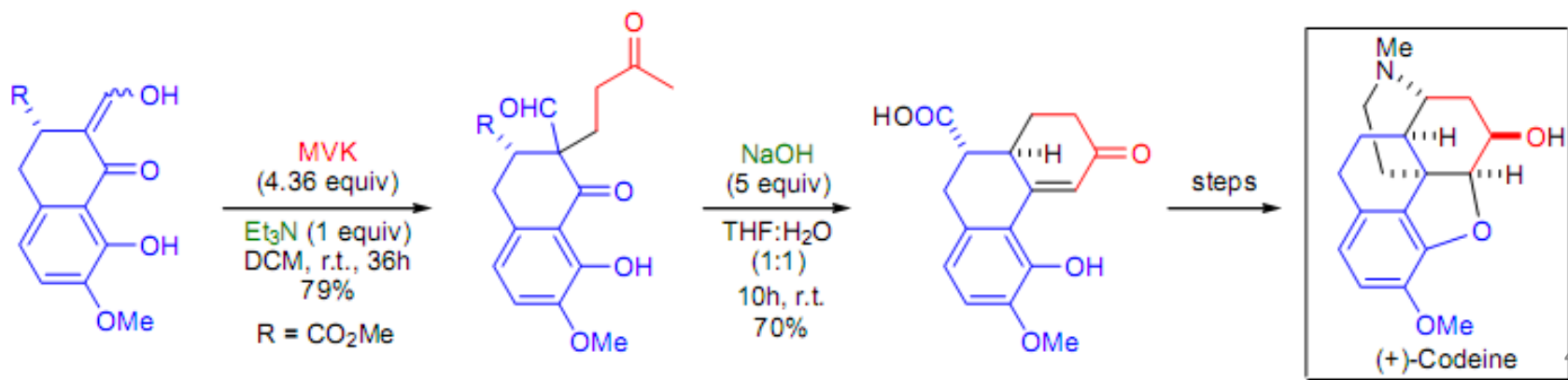


Synthetic Applications:

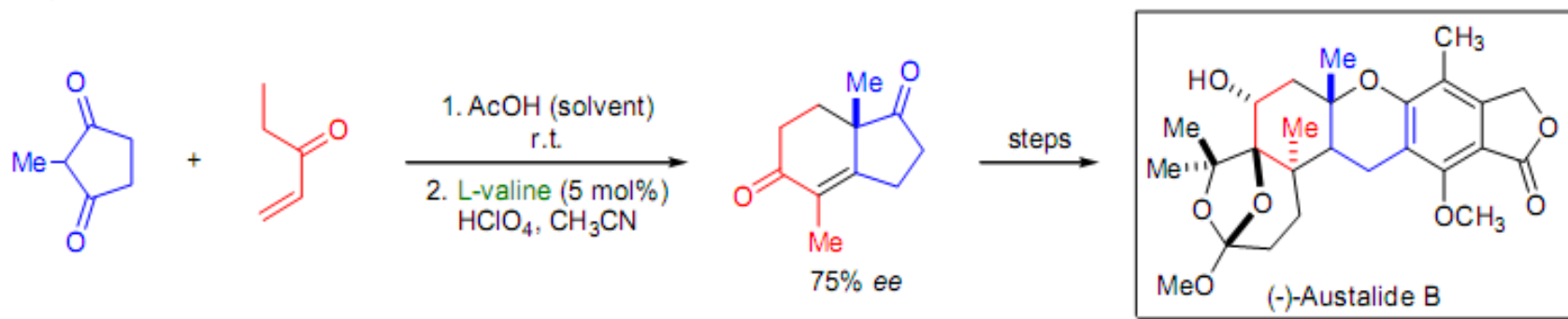
A *conjugate cuprate addition-Robinson annulation* sequence was utilized in the highly stereoselective total synthesis of **hispidospermidin** by S.J. Danishefsky et al.³⁷ It is a well-known fact that the MVK has a great tendency to polymerize under aprotic basic conditions that are used when the integrity of the enolate reaction partner has to be maintained. In order to avoid complications arising from the likely polymerization of MVK, α -trimethylsilyl methyl vinyl ketone (a base-stable surrogate of MVK developed by G. Stork and co-workers^{12,14}) was chosen as the reaction partner. The 2-substituted cyclopentenone was treated with lithium dimethyl cuprate, and the resulting enolate was trapped with α -trimethylsilyl MVK in a *Michael addition*. The crude Michael adduct was refluxed with aqueous KOH in methanol, which resulted in the desired hydrindenedione as a single diastereomer.



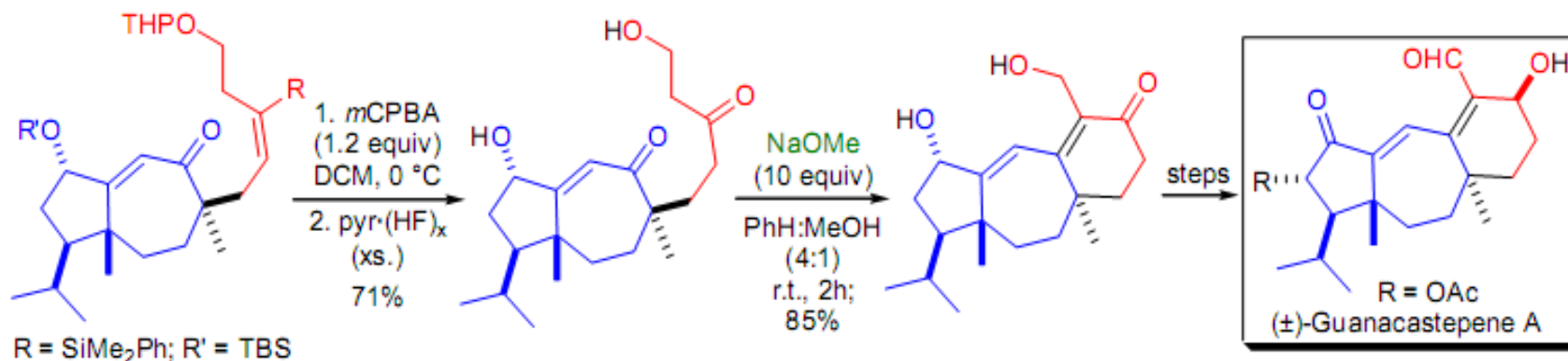
In the laboratory of J.D. White, the asymmetric total synthesis of (+)-codeine was accomplished.³⁸ The *Robinson annulation* was the method of choice to build a phenanthrenone precursor starting from a substituted tetralone derivative. As it is usually the case, the isolation of the Michael adduct allowed the *intramolecular aldol reaction* to proceed cleanly and to afford a higher yield of the annulated product.



The *Hajos-Parrish reaction* can be regarded as the enantioselective version of the *Robinson annulation*. In the early stages of the synthetic effort targeting the mixed polyketide-terpenoid metabolite (–)-austalide B, L.A. Paquette and co-workers used this transformation to prepare the key bicyclic precursor in enantiopure form.³⁹ Ethyl vinyl ketone was reacted with 2-methyl-1,3-cyclopentanedione in the presence of catalytic amounts of L-valine to afford the bicyclic diketone with a 75% ee.

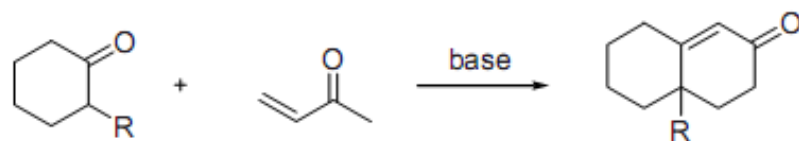


A novel variant of the *Stork-Jung modified Robinson annulation* was developed and applied to the formal total synthesis of (±)-guanacastepene A by the research group of B.B. Snider.⁴⁰ Instead of using MVK directly, they prepared the necessary 1,5-diketone by alkylating the ketone with an allylsilane and generating the ketone functionality via a *Fleming-Tamao oxidation*.

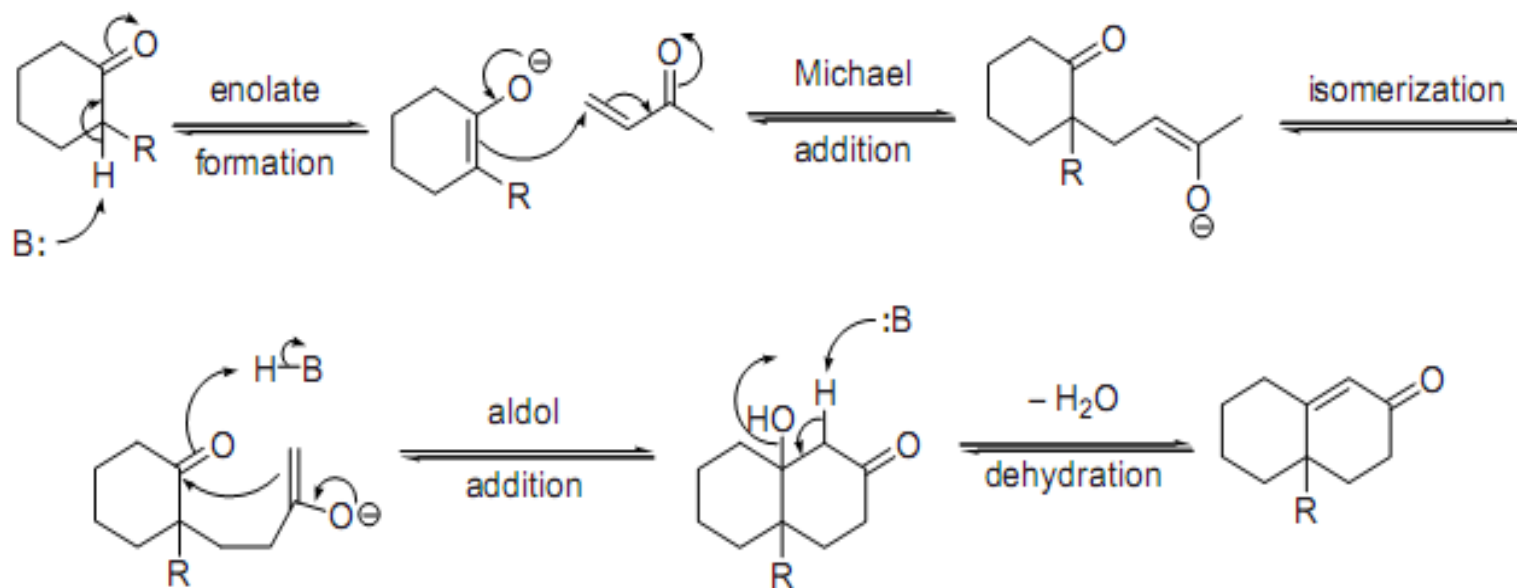


Robinson annulation

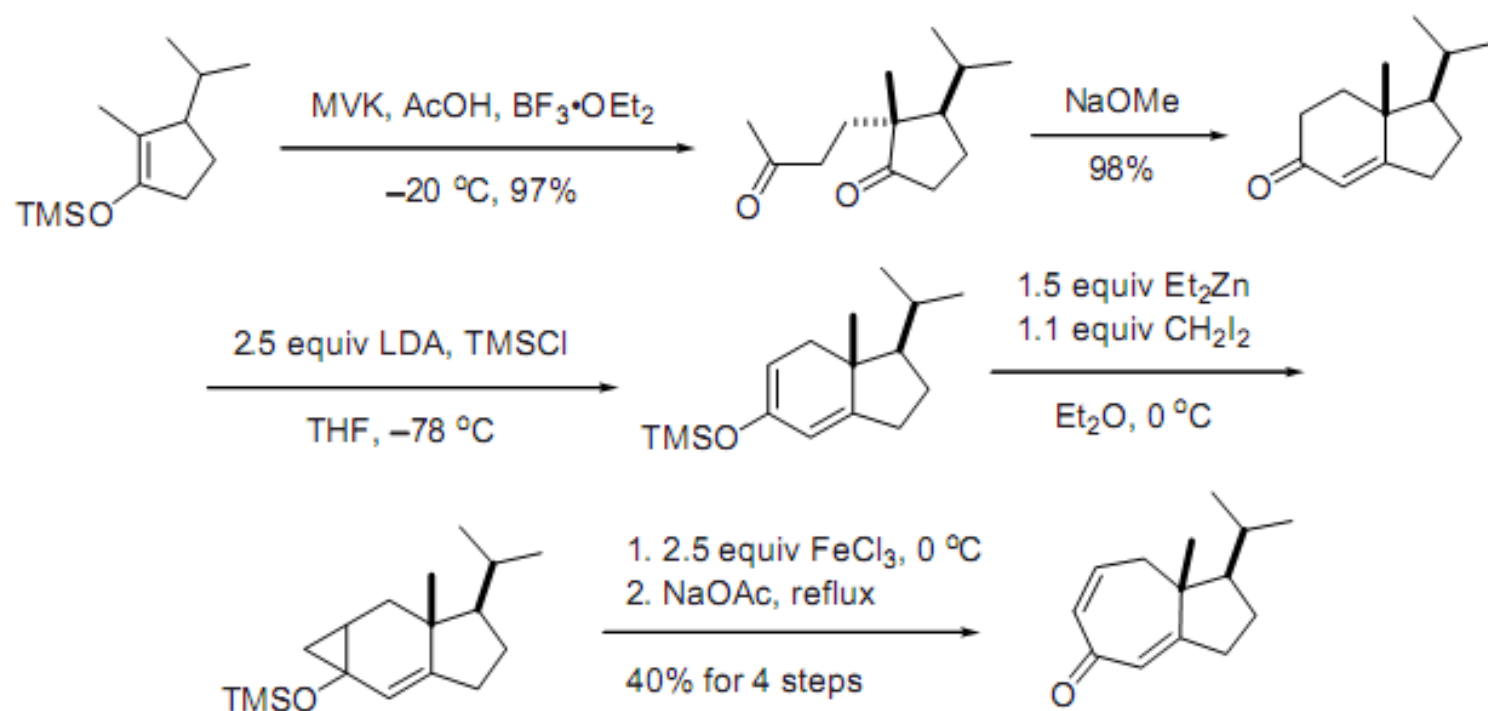
Michael addition of cyclohexanones to methyl vinyl ketone followed by intramolecular aldol condensation to afford six-membered α,β -unsaturated ketones.



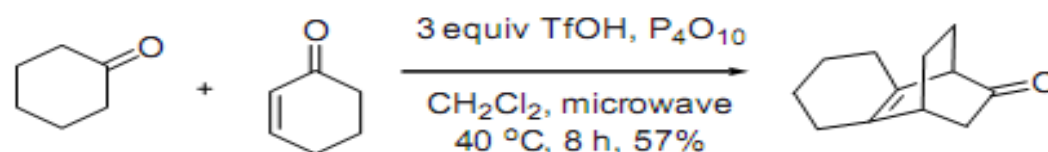
Mechanism



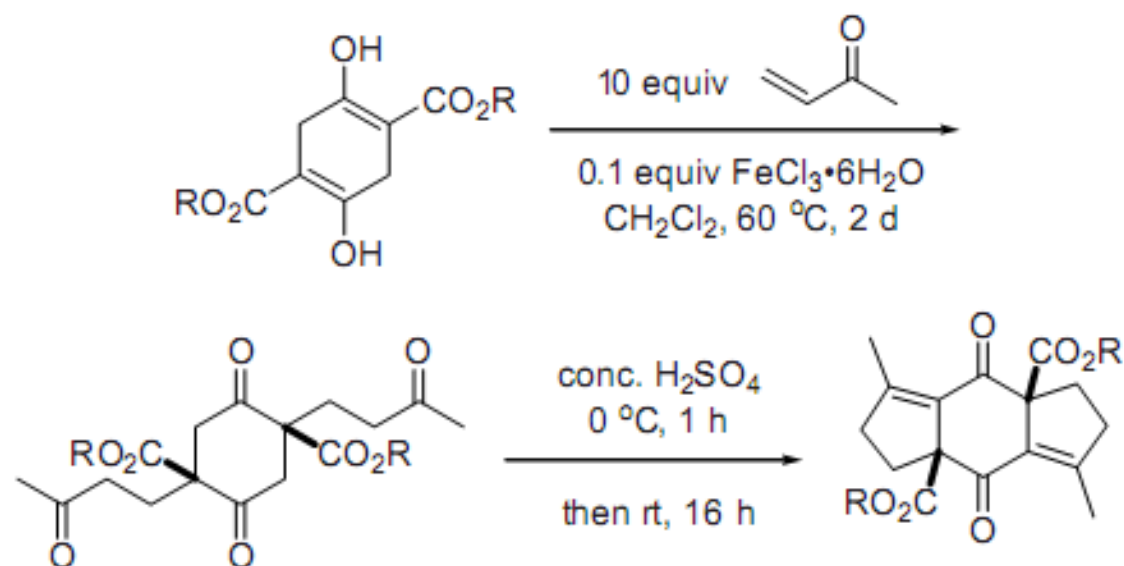
Example 1, Homo-Robinson⁷



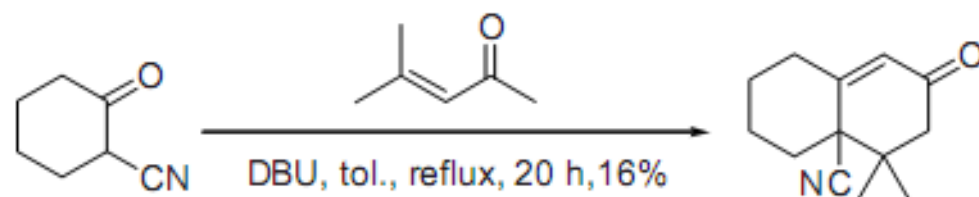
Example 2⁸



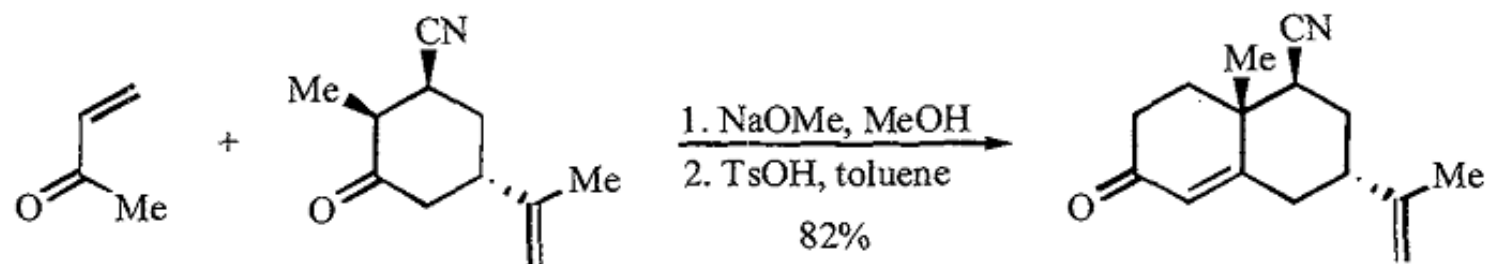
Example 3, Double Robinson-type cyclopentene annulation⁹



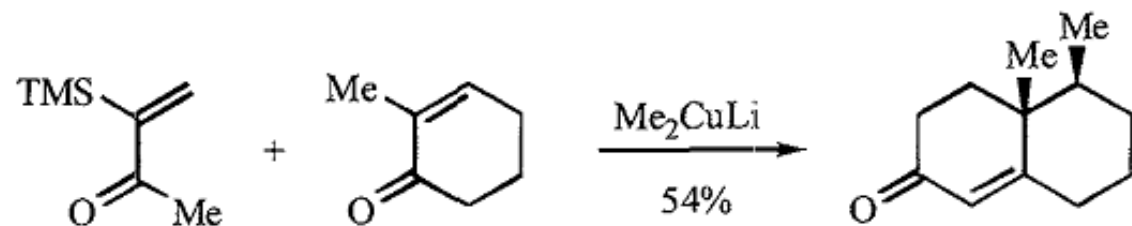
Example 4¹⁰



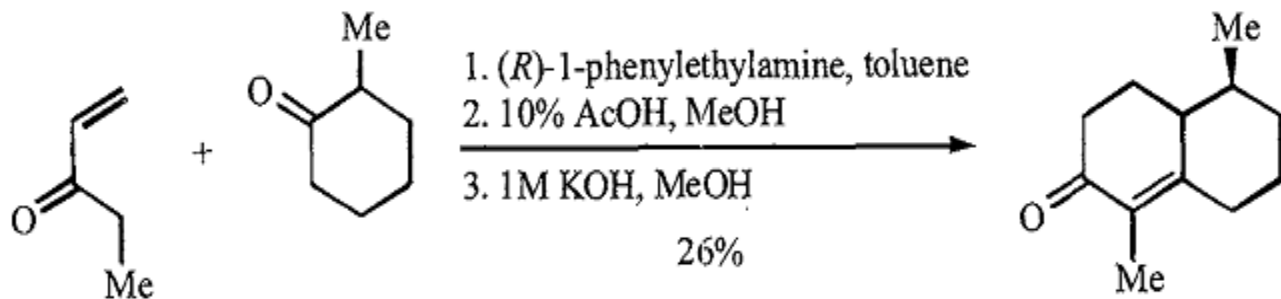
Examples:



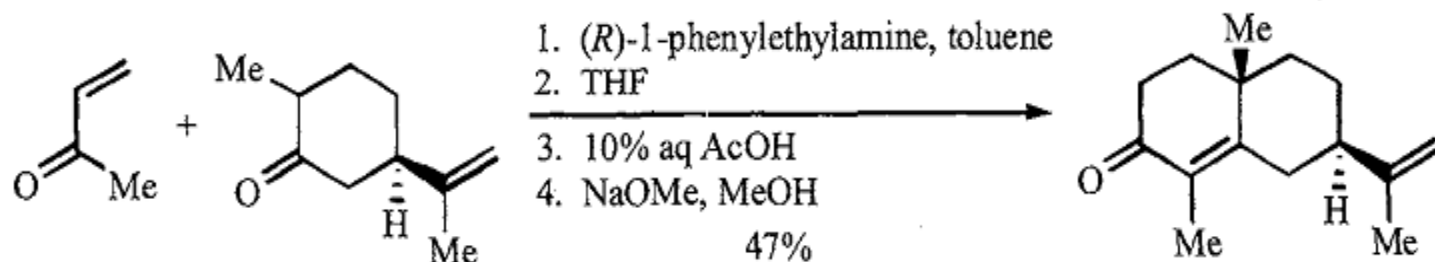
A. A. Verstegen-Haaksma, H. J. Swarts, J. M. B. Jansen, A. deGroot, *Tetrahedron* **1994**, 50, 10073



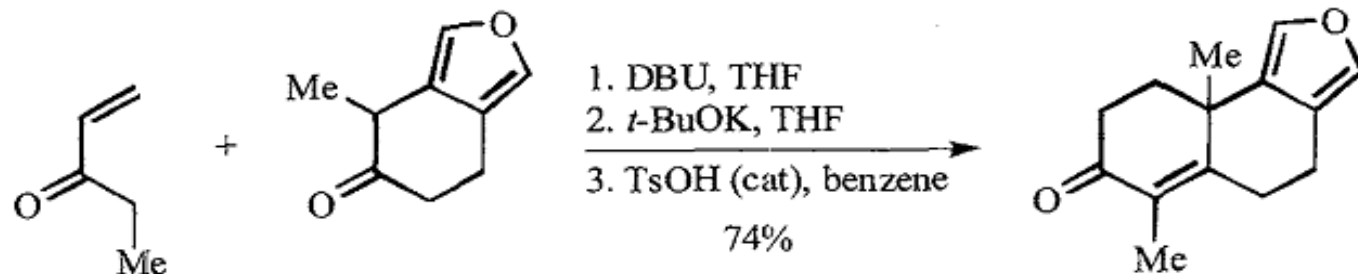
R. K. Boeckman, Jr., *Tetrahedron* **1983**, 39, 925



I. Jabin, G. Revial, K. Melloul, M. Pfau, *Tetrahedron: Asymmetry* **1997**, 8, 1101

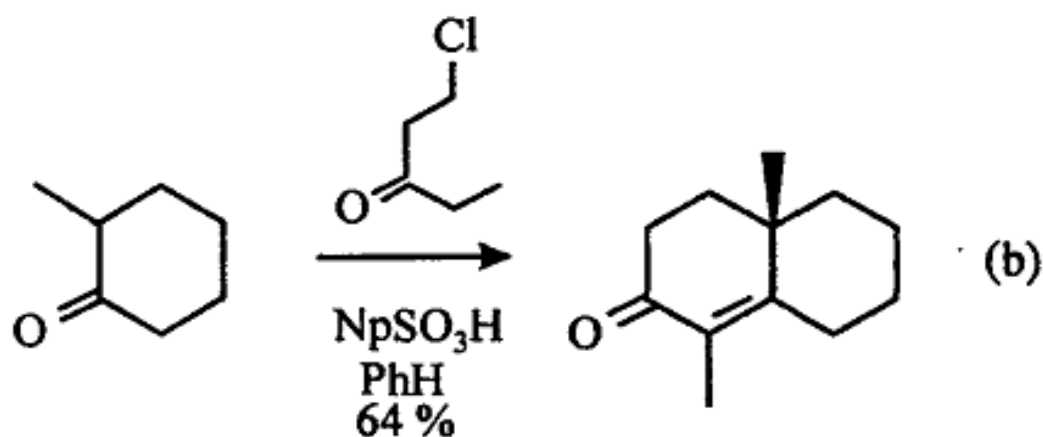
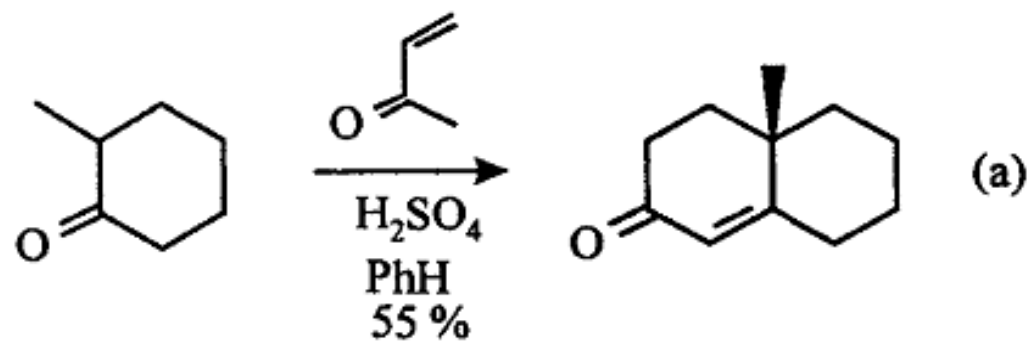


V. Zhabinskii, A. J. Minnaard, J. B. P. A. Wijnberg, A. deGroot, *Journal of Organic Chemistry* **1996**, 61, 4022



Y. Baba, T. Sakamoto, S. Soejima, K. Kanematsu, *Tetrahedron* **1994**, 50, 5645

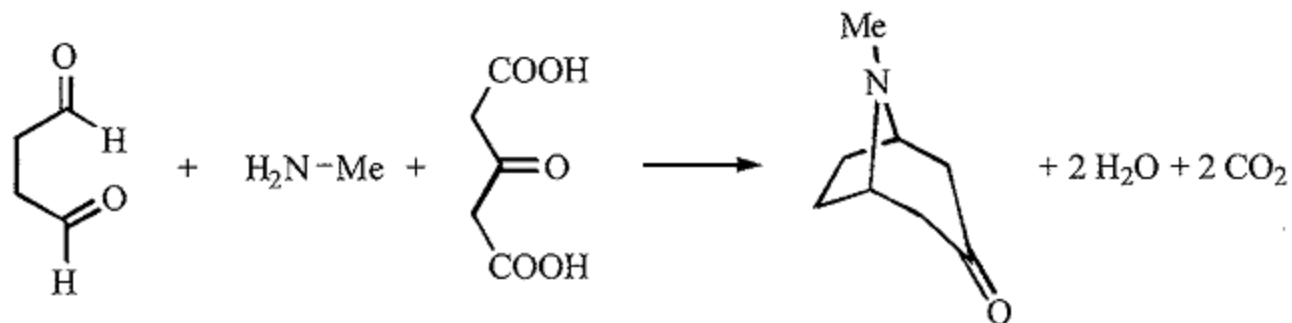
The Robinson Annulation can also proceed under acidic catalysis, with the entire process occurring in one pot, as shown below. The use of a precursor of the α,β -unsaturated ketone, such as a β -chloroketone, can reduce the steady-state concentration of enone and decrease the side reaction of polymerization.



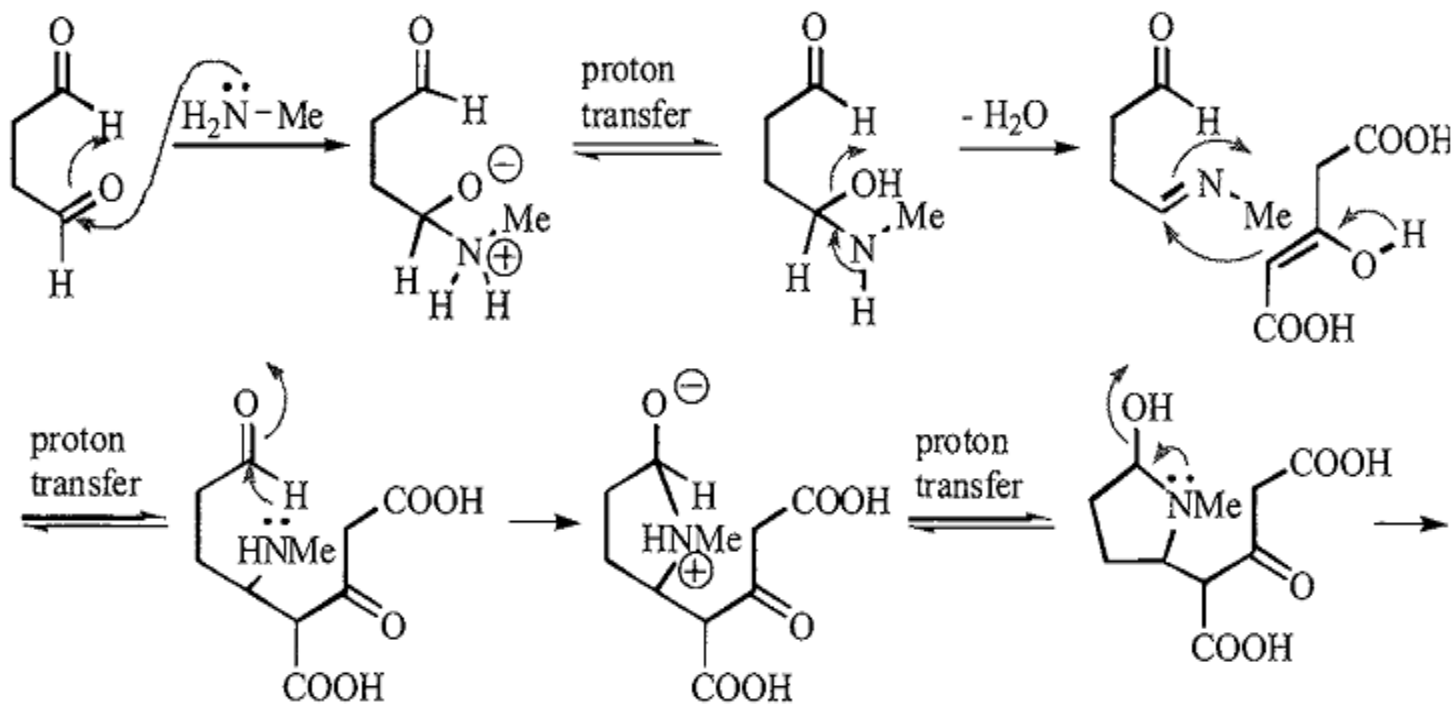
References

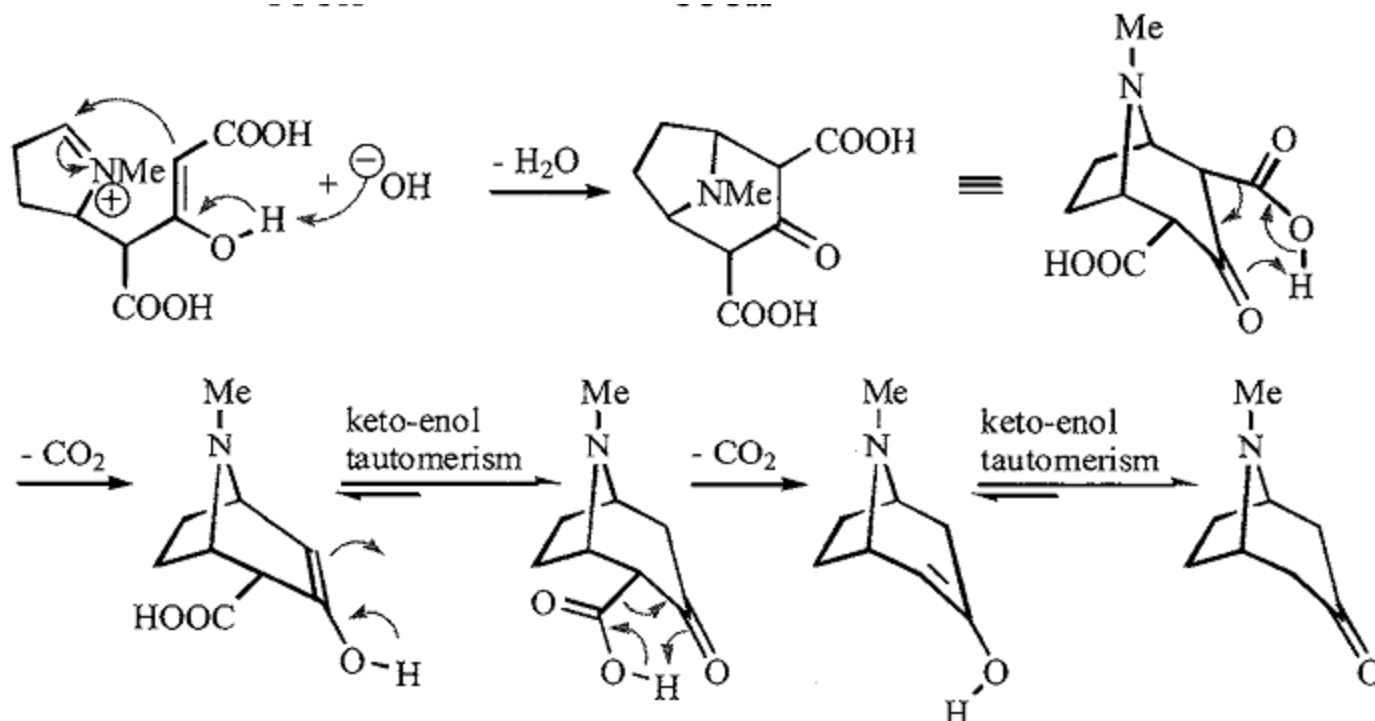
1. Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285–1288. Robert Robinson used the Robinson annulation in his total synthesis of cholesterol. Here is a story told by Derek Barton about Robinson and Woodward: “By pure chance, the two great men met early in a Monday morning on an Oxford train station platform in 1951. Robinson politely asked Woodward what kind of research he was doing these days; Woodward replied that he thought that Robinson would be interested in his recent total synthesis of cholesterol. Robinson, incensed and shouting ‘Why do you always steal my research topic?’, hit Woodward with his umbrella.”—An excerpt from Barton, Derek, H. R. *Some Recollections of Gap Jumping*, American Chemical Society, Washington, D.C., **1991**.
2. Gawley, R. E. *Synthesis* **1976**, 777–794. (Review).
3. Guarna, A.; Lombardi, E.; Machetti, F.; Occhiato, E. G.; Scarpi, D. *J. Org. Chem.* **2000**, *65*, 8093–8096.
4. Tai, C.-L.; Ly, T. W.; Wu, J.-D.; Shia, K.-S.; Liu, H.-J. *Synlett* **2001**, 214–217.
5. Jung, M. E.; Piizzi, G. *Org. Lett.* **2003**, *5*, 137–140.
6. Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, *70*, 739–741.
7. Yun, H.; Danishefsky, S. J. *Tetrahedron Lett.* **2005**, *46*, 3879–3882.
8. Jung, M. E.; Maderna, A. *Tetrahedron Lett.* **2005**, *46*, 5057–5061.
9. Zhang, Y.; Christoffers, J. *Synthesis* **2007**, 3061–3067.
10. Jahnke, A.; Burschka, C.; Tacke, R.; Kraft, P. *Synthesis* **2009**, 62–68.

Robinson-Schopf Reaction



Mechanism:

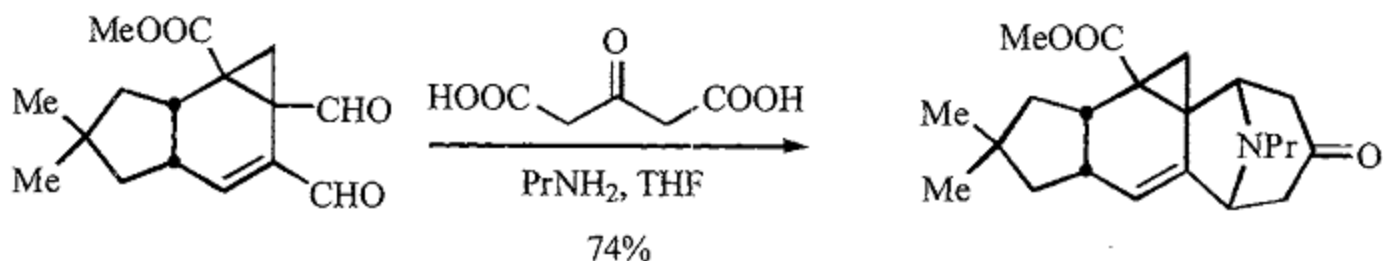




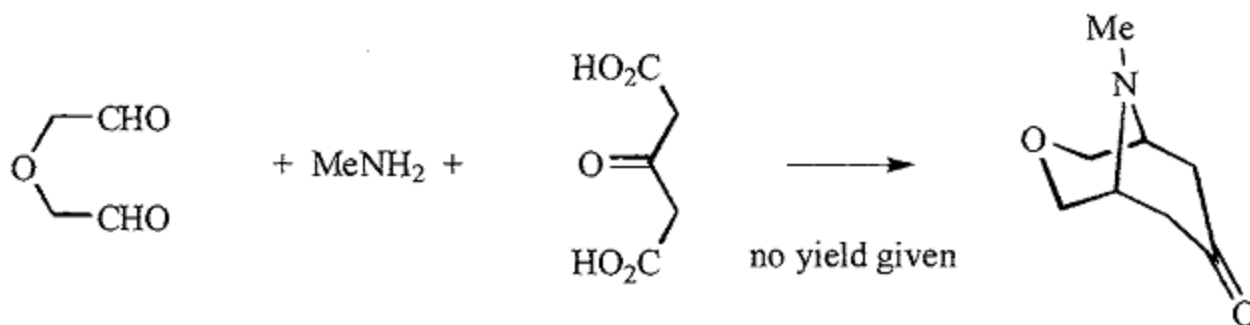
Notes:

This reaction is a “biomimetic” approach to forming alkaloids.

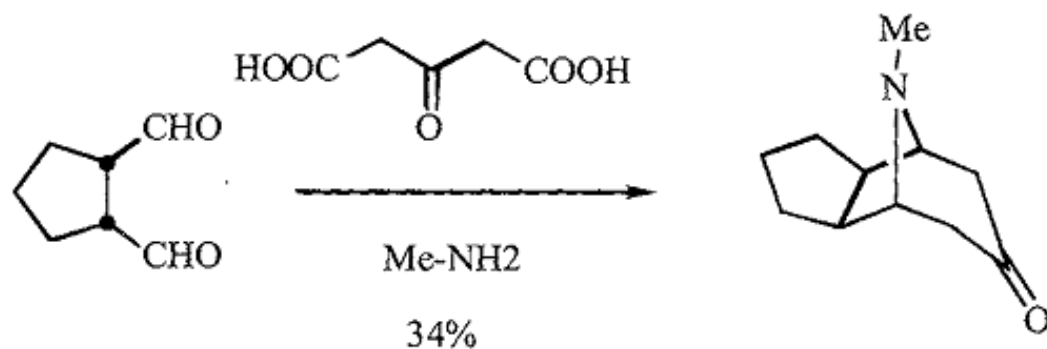
Examples:



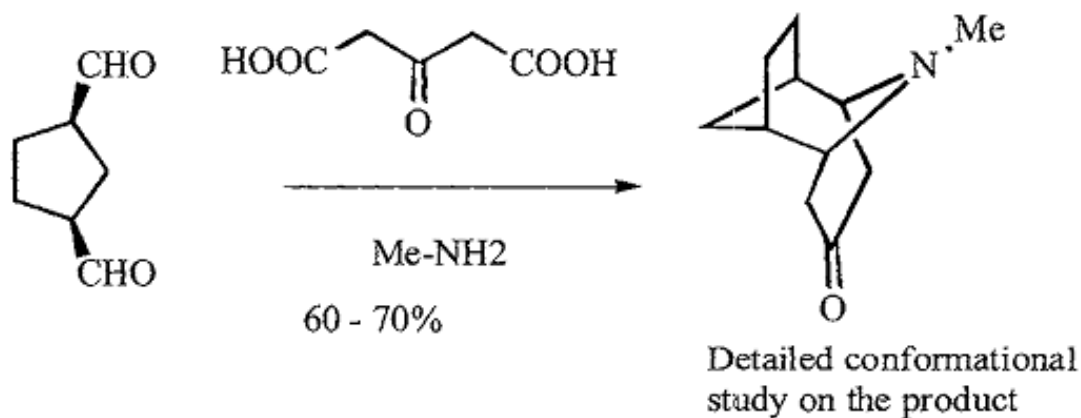
T. Jarevang, H. Anke, T. Anke, G. Erkel, O. Sterner, *Acta Chemica Scandinavica* **1998**, 52, 1350 (AN 1998:770310)



J. Bermudez, J. A. Gregory, F. D. King, S. Starr, R. J. Summersell, *Bioorganic and Medicinal Chemistry Letters* **1992**, 2, 519



O. L. Chapman, T. H. Koch, *Journal of Organic Chemistry* **1966**, 31, 1043



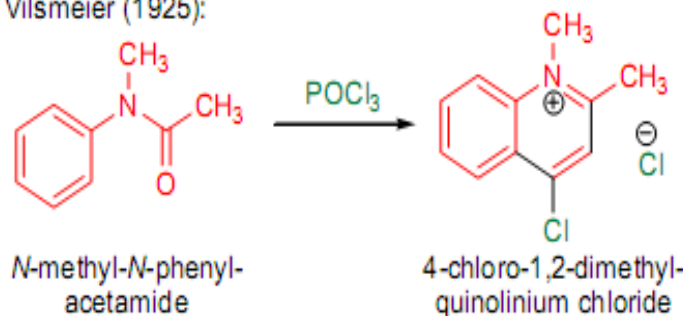
L. A. Paquette, J. W. Heimaster, *Journal of the American Chemical Society* **1966**, 88, 763

VILSMEIER-HAACK FORMYLATION

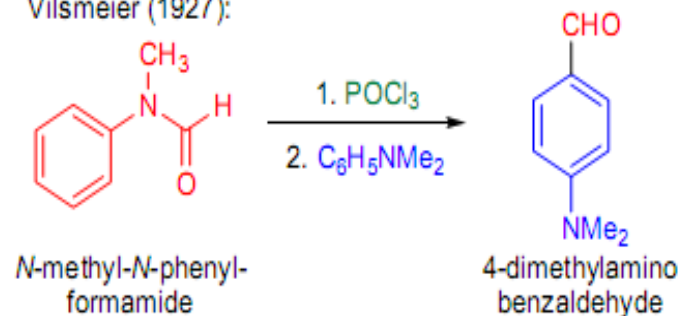
Importance:

In 1925, A. Vilsmeier and co-workers reported that upon treatment with phosphoryl chloride (POCl_3), *N*-methylacetanilide gave rise to a mixture of products among which 4-chloro-1,2-dimethylquinolinium chloride was one of the major products.¹ Further investigation revealed that the reaction between *N*-methylformanilide and POCl_3 gave rise to a chloromethyliminium salt (Vilsmeier reagent), which readily reacts with electron-rich aromatic compounds to yield substituted benzaldehydes.² The introduction of a formyl group into electron-rich aromatic compounds using a Vilsmeier reagent is known as the *Vilsmeier-Haack formylation* (*Vilsmeier reaction*). The general features of this transformation are:^{8,11} 1) the Vilsmeier reagent is prepared from any *N,N*-disubstituted formamide by reacting it with an acid chloride (e.g., POCl_3 , SOCl_2 , oxalyl chloride); 2) most often the combination of DMF and POCl_3 is used and the resulting Vilsmeier reagent is usually isolated before use; 3) mostly electron-rich aromatic or heteroaromatic compounds⁸ as well as electron-rich alkenes and 1,3-dienes¹¹ are substrates for the transformation, since the Vilsmeier reagent is a weak electrophile; 4) the relative reactivity of five-membered heterocycles is pyrrole > furan > thiophene; 5) the solvent is usually a halogenated hydrocarbon, DMF or POCl_3 and the nature of the solvent has a profound effect on the electrophilicity of the reagent, so it should be carefully chosen; 6) the required reaction temperature varies widely depending on the reactivity of the substrate and it ranges from below 0 °C up to 80 °C; 7) the initial product is an iminium salt, which can be hydrolyzed with water to the corresponding aldehyde, treated with H_2S to afford thioaldehydes, reacted with hydroxylamine to afford nitriles, or reduced to give amines; 8) the transformation is regioselective favoring the less sterically hindered position (this means the *para* position on a substituted benzene ring); but electronic effects can also influence the product distribution; and 9) vinylogous chloromethyliminium salts undergo similar reaction to afford the corresponding α,β -unsaturated carbonyl compounds upon hydrolysis.

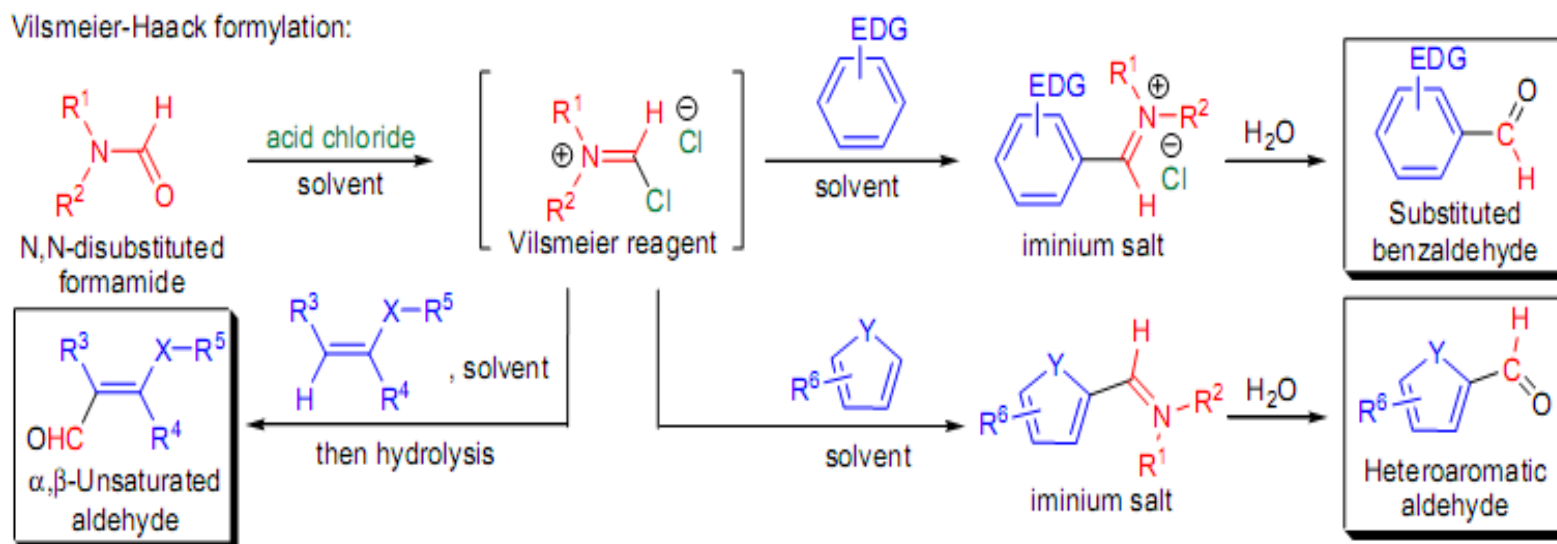
Vilsmeier (1925):



Vilsmeier (1927):



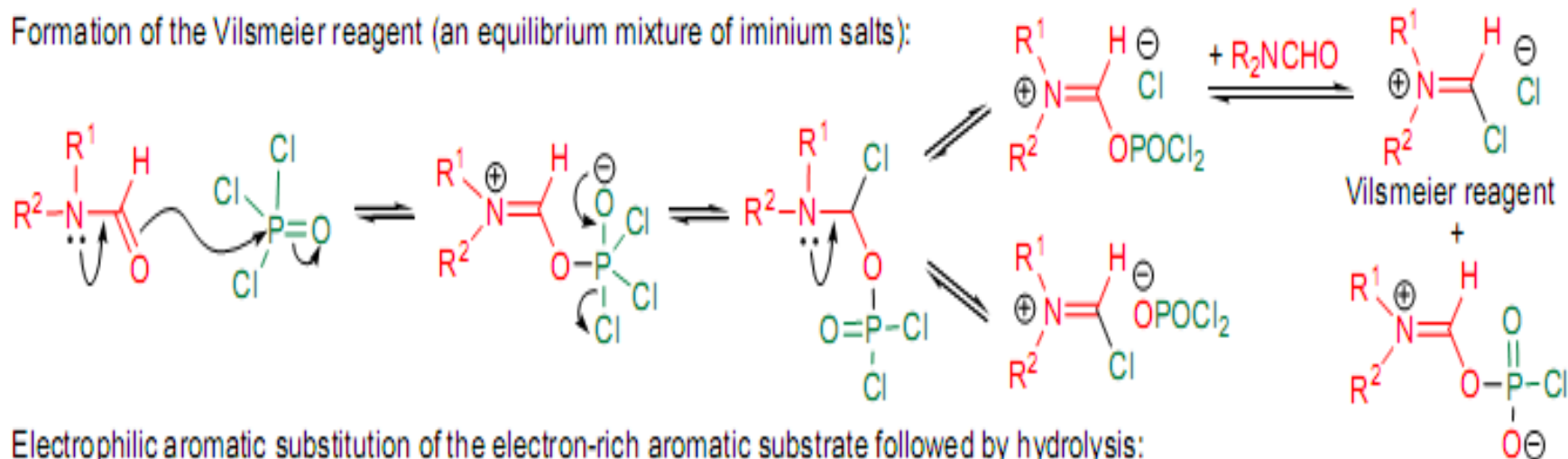
Vilsmeier-Haack formylation:



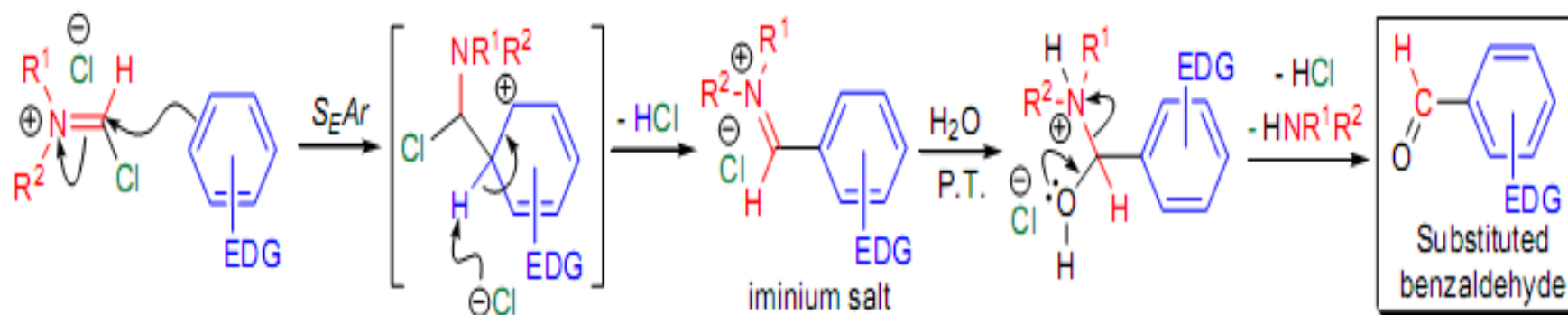
R^{1-2} = alkyl, aryl; acid chloride: POCl_3 , SOCl_2 , COCl_2 , $(\text{COCl})_2$, Ph_3PBr_2 , 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, POCl_3 ;
EDG = OH, O-alkyl, O-aryl, NR_2 ; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH_2 , CR_2 ; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

Mechanism:

Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):

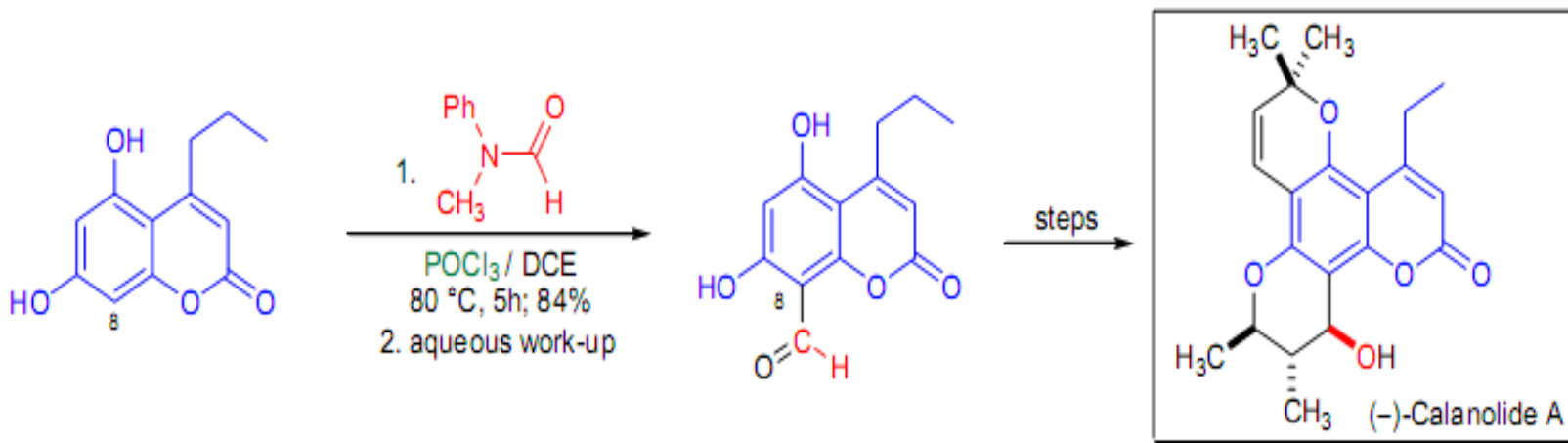


Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:

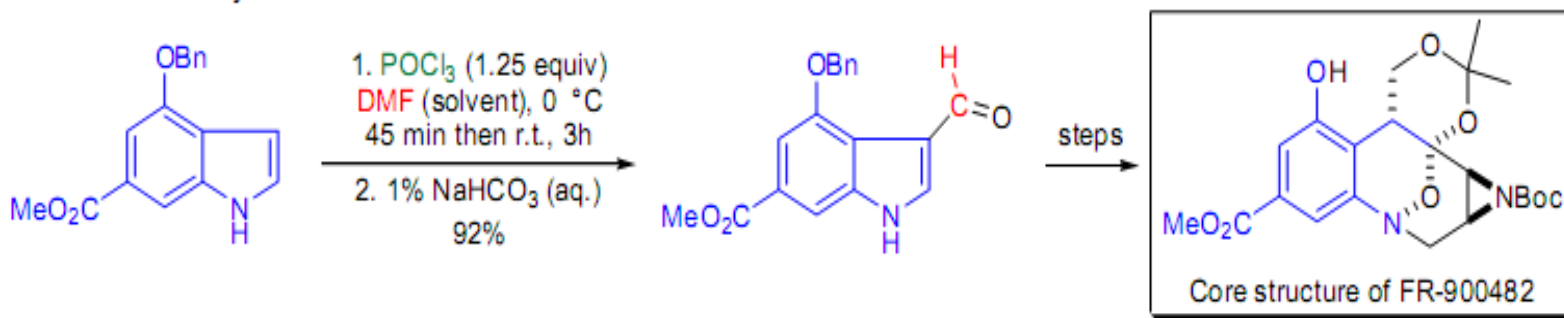


Synthetic Applications:

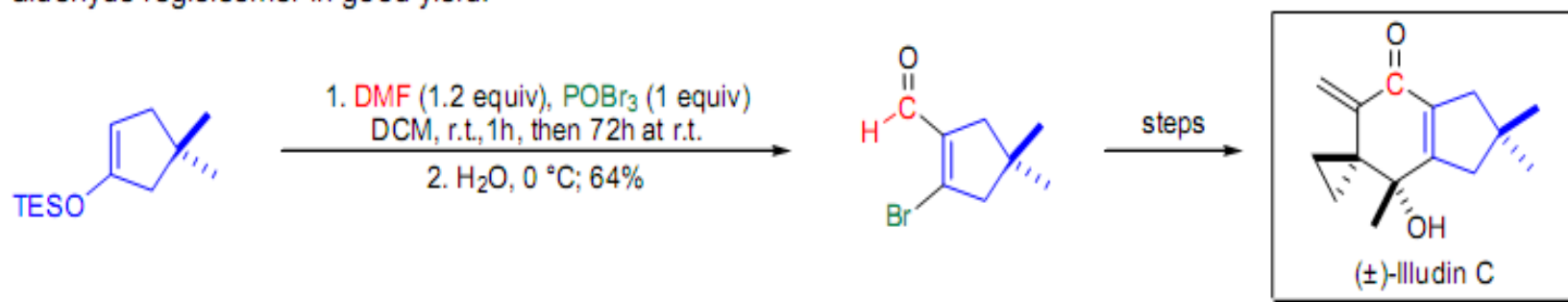
The total synthesis of the calophyllum coumarin (-)-calanolide A was accomplished by D.C. Baker and co-workers.⁴³ This compound attracted considerable attention because it is a potent inhibitor of HIV-1 reverse transcriptase. In order to introduce a formyl group at C8, a regioselective *Vilsmeier reaction* was employed on a coumarin lactone substrate.



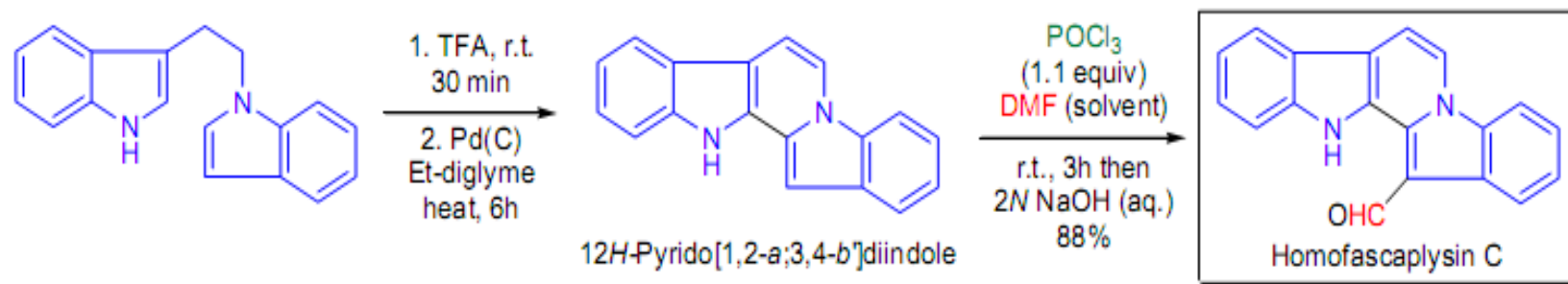
In the laboratory of F.E. Ziegler, the cyclization of a chiral aziridinyl radical into an indole nucleus was utilized to prepare the core nucleus of the potent antitumor agent FR-900482.⁴⁴ In the early stages of the synthetic effort, the *Vilsmeier-Haack formylation* was chosen to install an aldehyde functionality at the C3 position of a substituted indole substrate. The initial iminium salt was hydrolyzed under very mildly basic conditions to minimize the hydrolysis of the methyl ester moiety. Eventually the formyl group was removed from the molecule *via decarbonylation* using Wilkinson's catalyst.



Since the *Vilsmeier-Haack formylation* is feasible on electron-rich alkenes such as enol ethers, it was a method of choice to prepare an α,β -unsaturated aldehyde during the total synthesis of (\pm)-illudin C by R.L. Funk et al.⁴⁵ The TES enol ether was treated with several reagent combinations (e.g., $\text{PBr}_3/\text{DMF}/\text{DCM}$), but unfortunately only regioisomeric product mixtures were obtained. However, the use of $\text{POBr}_3/\text{DMF}/\text{DCM}$ allowed the clean preparation of the desired aldehyde regioisomer in good yield.



The marine sponge pigment **homofascaplysin C** was synthesized by the research team of G.W. Gribble.⁴⁶ The natural product had a novel 12*H*-pyrido[1,2-*a*:3,4-*b'*]diindole ring system and a formyl group at the C13 position. The *Vilsmeier reaction* allowed the introduction of this substituent in excellent yield.



The total synthesis of (-)-(*R*)-MEM-protected arthrographol was accomplished by G.L.D. Krupadanam et al.⁴⁷ The authors used sequential *Vilsmeier reaction/Dakin oxidation* to prepare a 1,2,4-trihydroxybenzene derivative.

