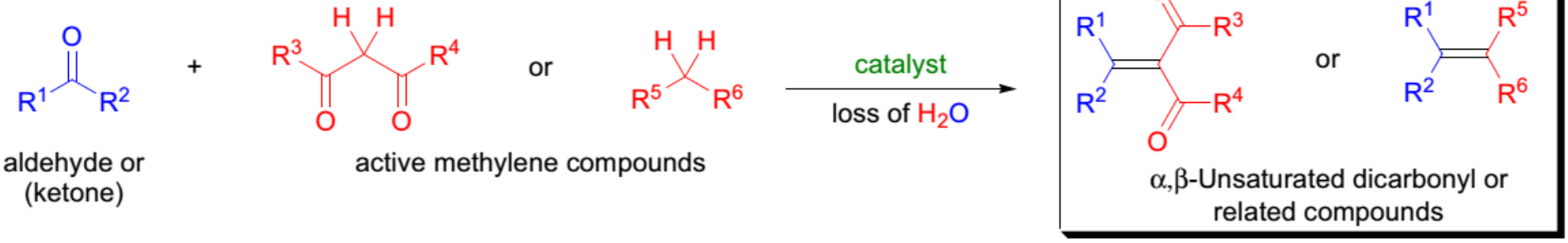
KNOEVENAGEL CONDENSATION

Knoevenagel condensation:

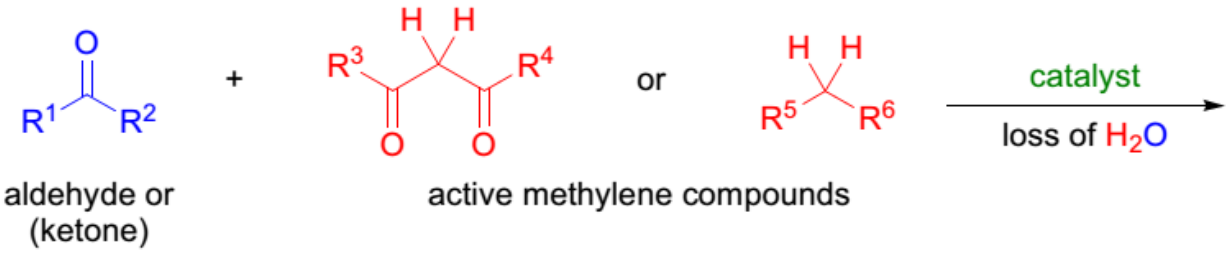


aldehyde or (ketone)

active methylene compounds

α,β-Unsaturated dicarbonyl or related compounds

Knoevenagel condensation:



aldehyde or (ketone)

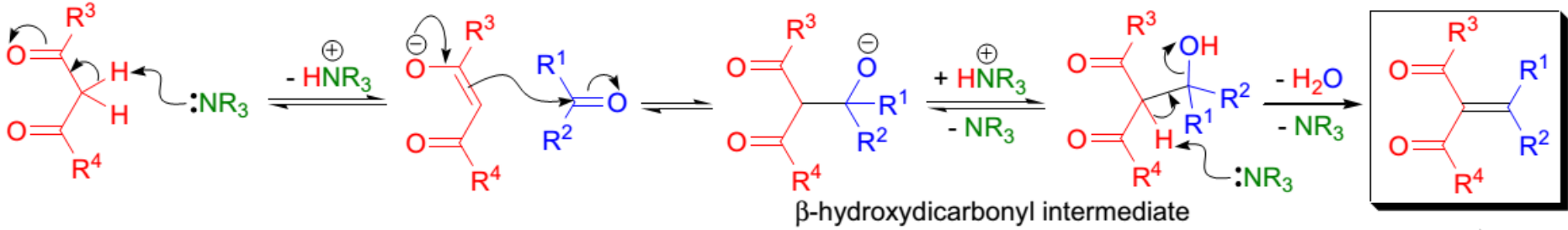
active methylene compounds

α,β-Unsaturated dicarbonyl or related compounds

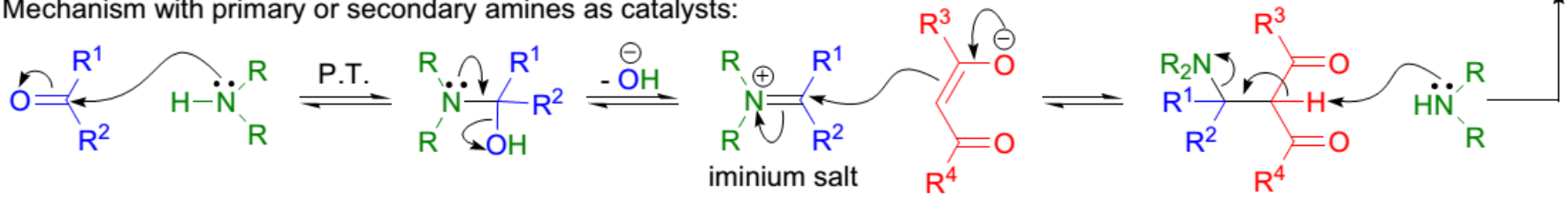
- The nature of the catalyst is important, usually primary, secondary, and tertiary amines and their corresponding ammonium salts, certain Lewis acids combined with a tertiary amine (e.g., TiCl4/Et3N), or other inorganic compounds such as aluminum phosphate are used;
- The choice of solvent is crucial and the use of dipolar aprotic solvents (e.g., DMF) is advantageous, since protic solvents inhibit the last 1,2-elimination step;
- The dicarbonyl product can be hydrolyzed and decarboxylated to afford the corresponding α,β-unsaturated carbonyl compounds;
- When R3 and R4 or R5 and R6 are different, the product is obtained as a mixture of geometrical isomers, and the selectivity is dictated by steric effects;
- Usually the thermodynamically more stable compound is formed as the major product.

Mechanism

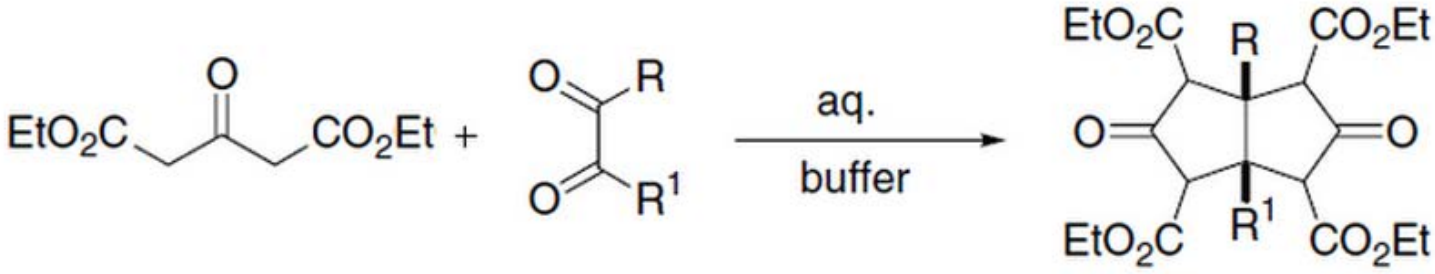
Hann-Lapworth mechanism with tertiary amines as catalysts:



Mechanism with primary or secondary amines as catalysts:

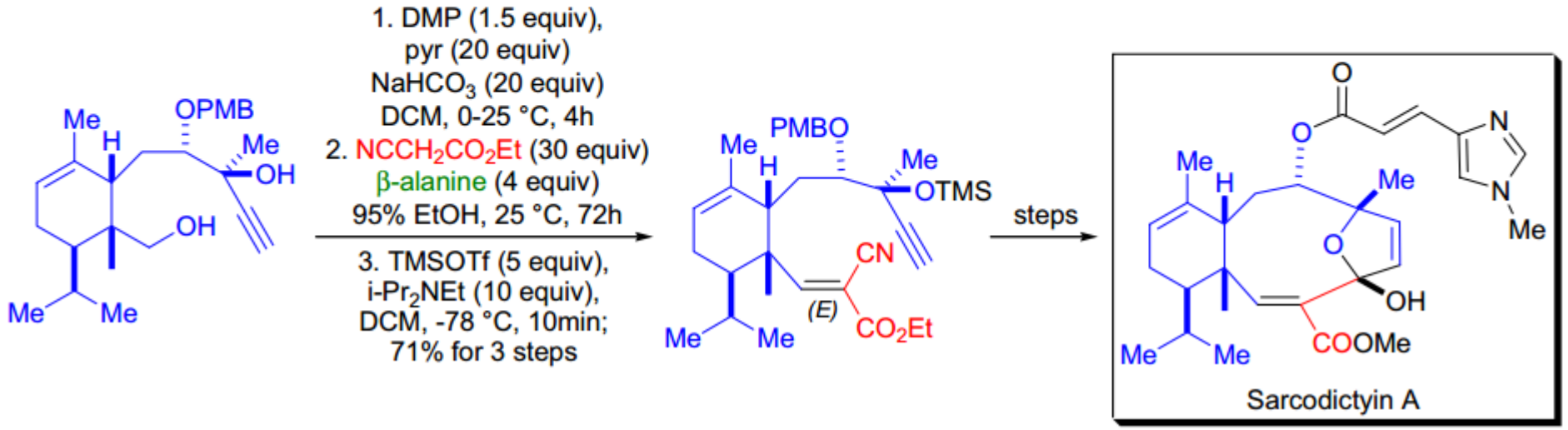


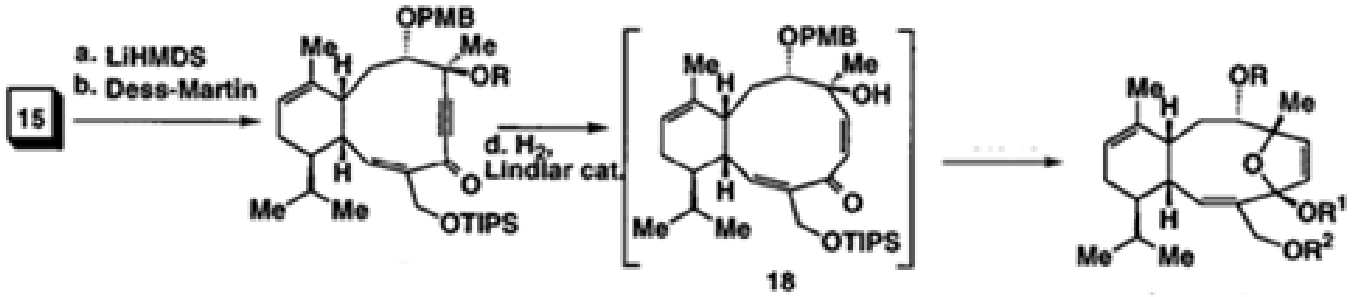
Weiss–Cook reaction



Synthetic Applications

The total synthesis of the marine-derived diterpenoid sarcodictyin A was accomplished in the laboratory of K.C. Nicolaou.[56] The most challenging part of the synthesis was the construction of the tricyclic core, which contains a 10-membered ring. This macrocycle was obtained by the intramolecular 1,2-addition of an acetylide anion to an α,β-unsaturated aldehyde. This unsaturated aldehyde moiety was installed by utilizing the *Knoevenagel condensation* catalyzed by β-alanine. The Knoevenagel product was exclusively the (*E*)-cyanoester.





Synthetic Applications

The domino *Knoevenagel condensation/hetero-Diels-Alder reaction* was used for the enantioselective total synthesis of the active anti-influenza A virus indole alkaloid hirsutine and related compounds by L.F. Tietze and co-workers.[57] The *Knoevenagel condensation* was carried out between an enantiopure aldehyde and Meldrum's acid in the presence of ethylenediamine diacetate. The resulting highly reactive 1-oxa-1,3-butadiene underwent a *hetero-Diels-Alder reaction* with 4-methoxybenzyl butenyl ether (*E*/*Z* = 1:1) *in situ*. The product exhibited a 1,3-asymmetric induction greater than 20:1.