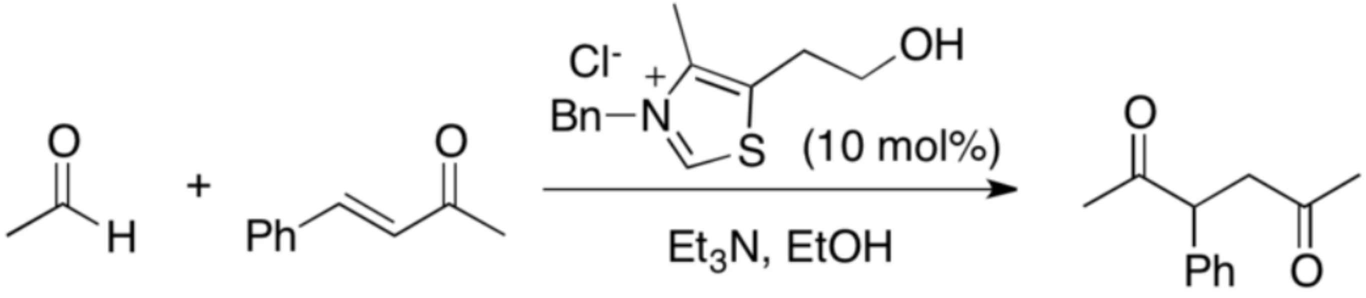
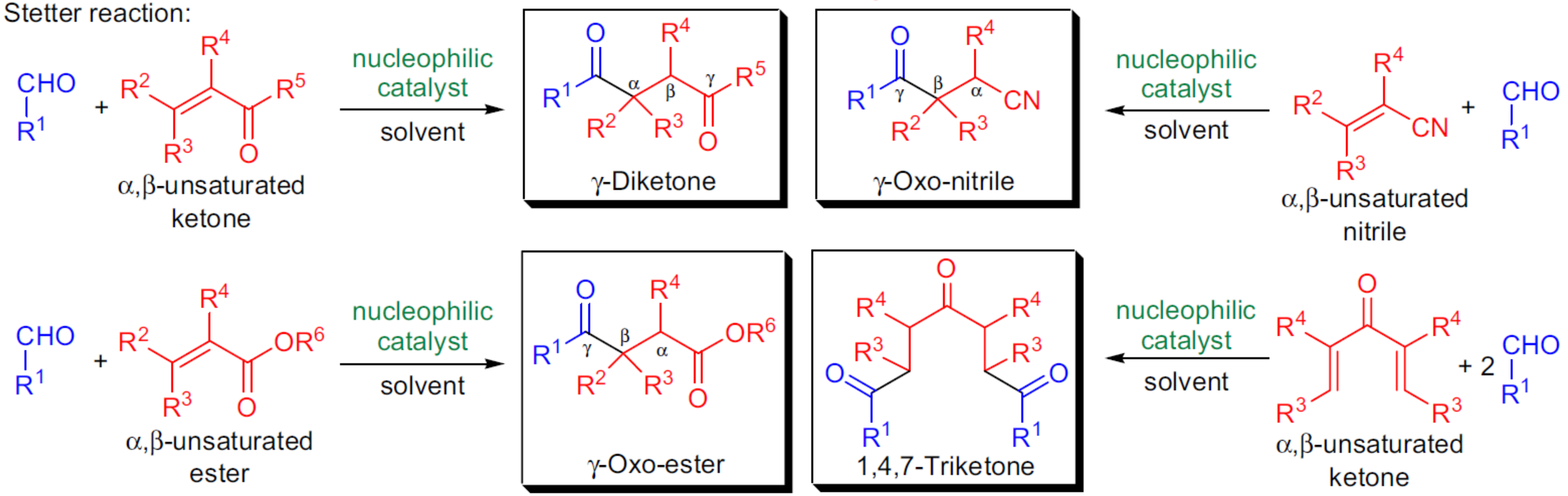
Stetter Reaction



H. Stetter

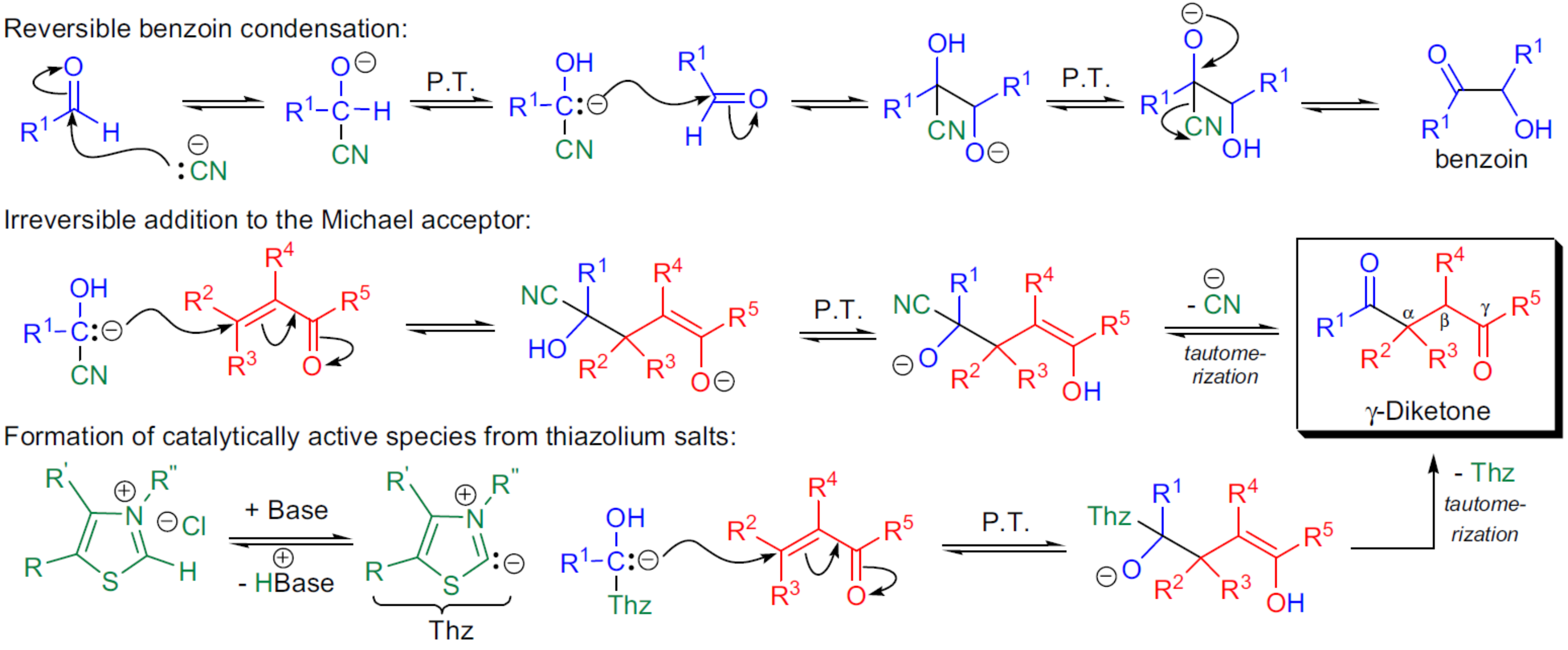
Hermann Stetter (1917–1993)

Stetter reaction:



R^1 = alkyl, aryl, heteroaryl, alkenyl; $R^{2\text{-}5}$ = H, alkyl, aryl, heteroaryl; R^6 = alkyl, aryl; nucleophilic catalyst: NaCN, KCN, thiazolium salts/base; solvent: DMF, DMSO

Mechanism: [2,5]


Reversible benzoin condensation:

Irreversible addition to the Michael acceptor:

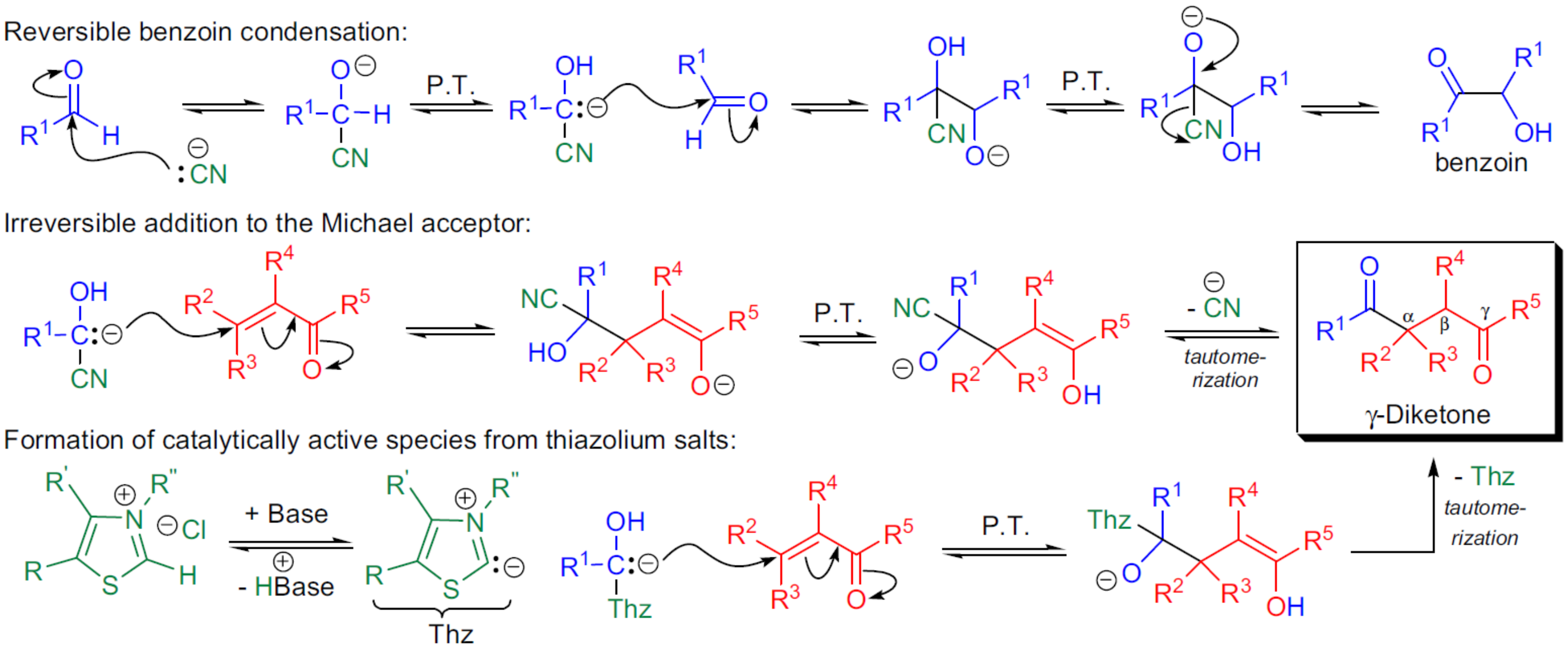
Formation of catalytically active species from thiazolium salts:

1) when the reaction is catalyzed by cyanide ions, dipolar aprotic solvents (e.g., DMF, DMSO) should be used, but with thiazolium salts protic solvents (e.g. EtOH) may also be used.

2) the reaction temperature is usually above 30 °C and the reaction time is a few hours (~1-4h).

3) the cyanide catalyzed reaction is restricted to aromatic aldehydes, since aliphatic aldehydes undergo an undesired *aldol condensation.*

Mechanism:[2,5]



Reversible benzoin condensation:

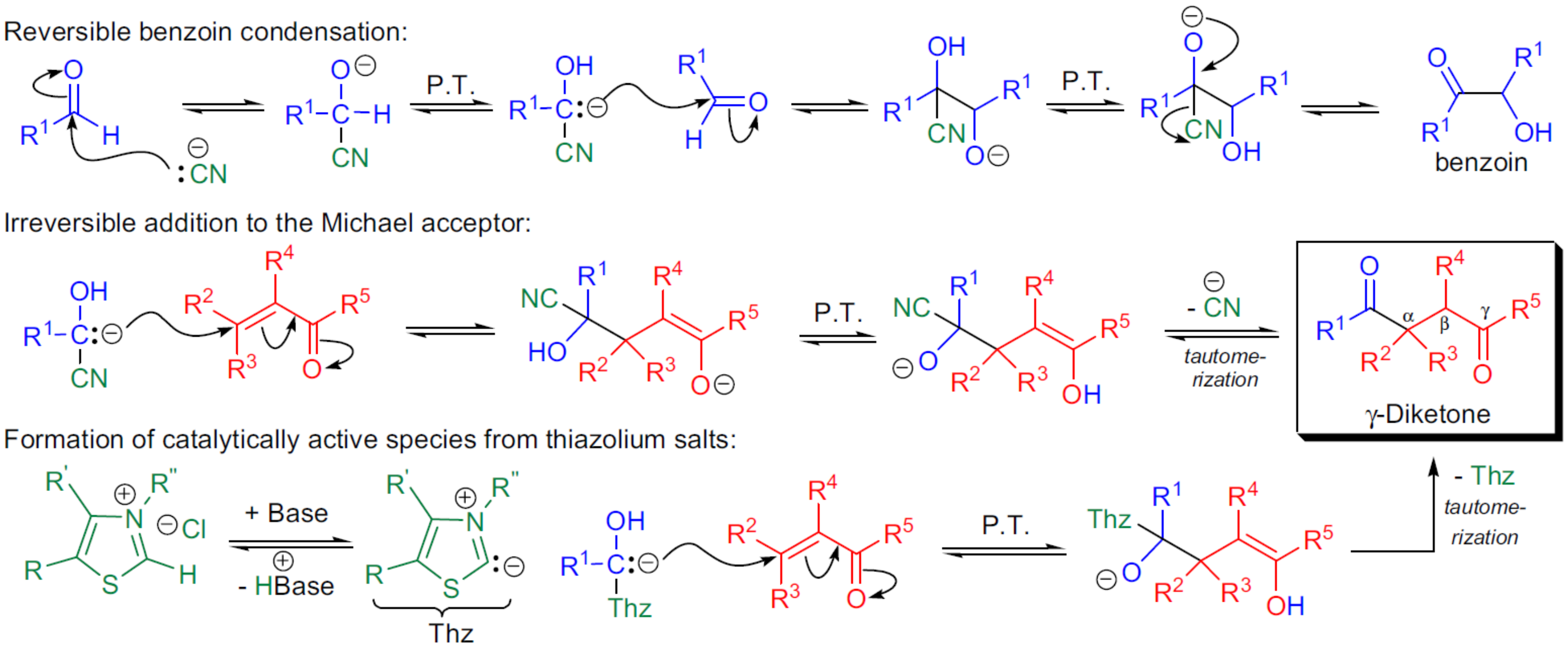
Irreversible addition to the Michael acceptor:

Formation of catalytically active species from thiazolium salts:

4) the thiazolium salts are actually precatalysts since the added base (e.g., Et3N, NaOAc) deprotonates the highly acidic C-H bond between the nitrogen and sulfur atoms to generate an ylide structure *in situ* (this ylide behaves the same way as cyanide ions do);

5) since the mechanism involves the rapid, reversible formation of benzoins from aromatic aldehyde substrates, benzoins can be used instead of the aldehydes (aliphatic aldehydes cannot be replaced with acyloins)

Mechanism: [2,5]


Reversible benzoin condensation:

Irreversible addition to the Michael acceptor:

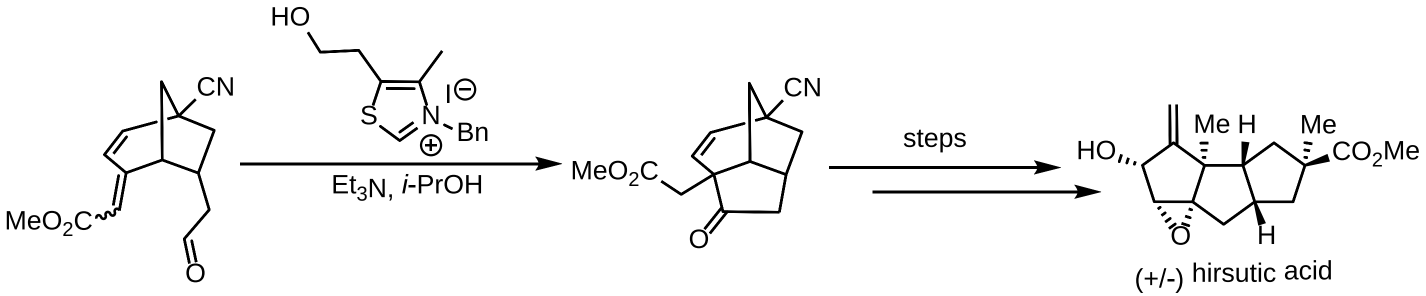
Formation of catalytically active species from thiazolium salts:

6) a wide variety of activated alkene substrates can be used, and the yields are especially high with α,β-unsaturated ketones.

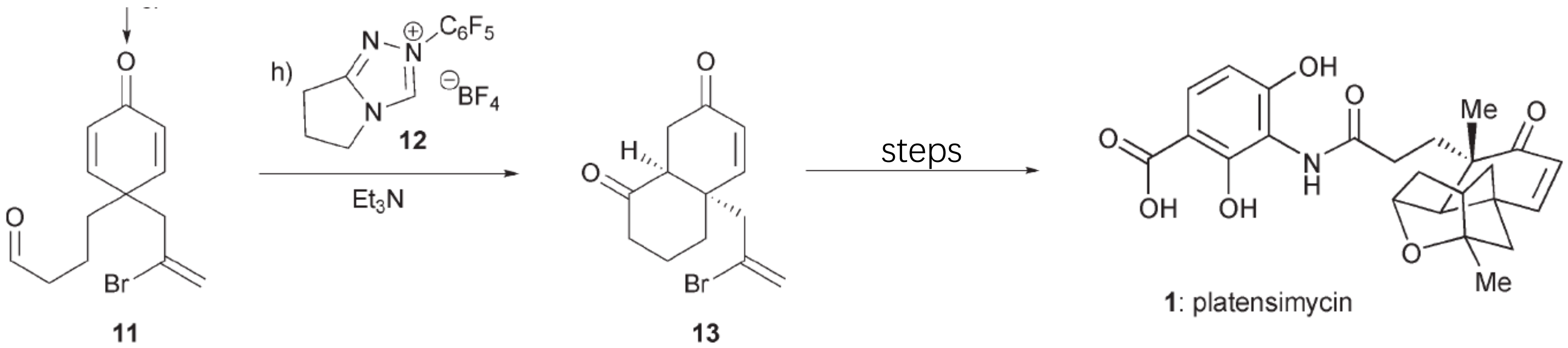
7) straight chain aldehydes tend to give higher yields than α-branched aldehydes

8) the aldehyde substrates may also be α,β-unsaturated and may have isolated double or triple bonds

9) the reaction fails with aromatic aldehydes that have nitro substituents as well as with 2,6-disubstituted aromatic aldehydes (due to steric hindrance)

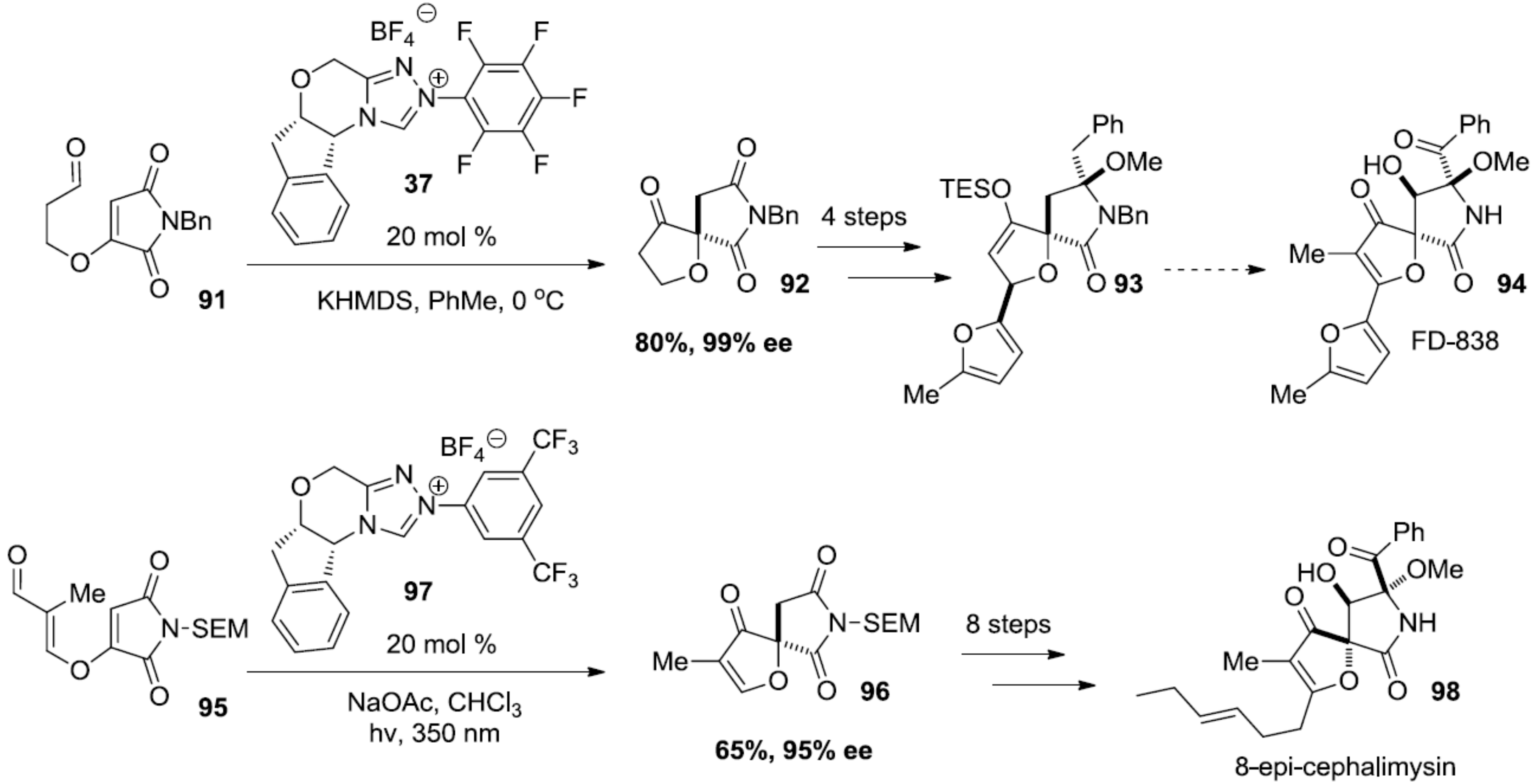


(+/-) hirsutic acid
Barry M. Trost
J. Am. Chem. Soc., 1979, 101 (5), pp 1284-1285



1: platensimycin

K. C. Nicolaou
Chem. Commun., 2007, 1922–1923



Stephen P. Lathrop and Tomislav Rovis
Chem. Sci., **2013,4, 1668-1673**

David Michael Rubush

DISSERTATION: PROGRESS TOWARD THE TOTAL SYNTHESIS OF STEMOCURTISINE AND ASYMMETRIC SYNTHESIS OF ENDOPEROXIDE ANTICANCER AGENTS VIA BRØNSTED ACID CASCADE CATALYSIS

Thanks !