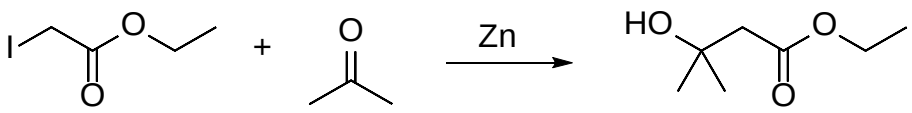
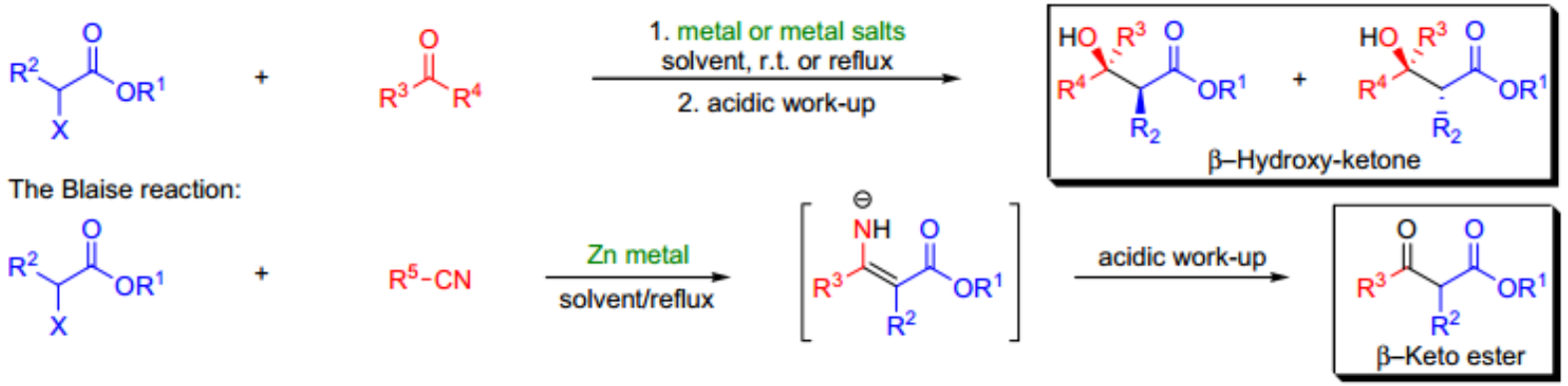
Reformatsky reaction



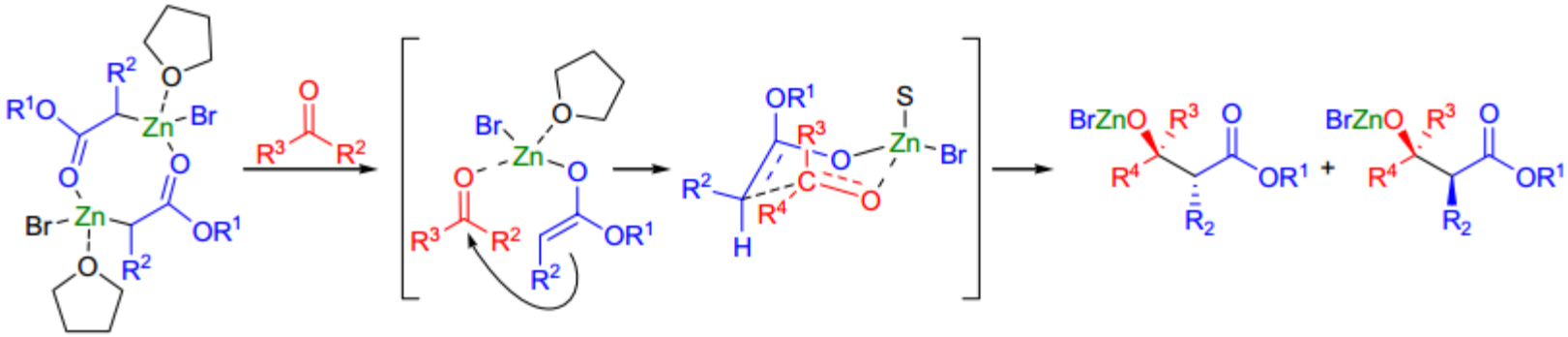
S. Reformatsky, 1887

1901



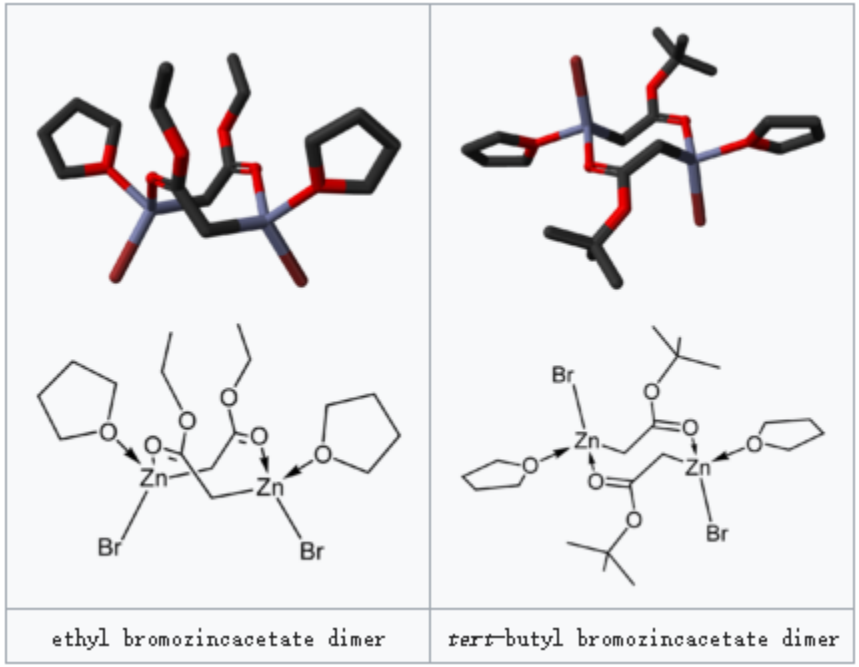
X = Cl, Br, I; R^1 = alkyl; R^2 = H, alkyl, aryl; R^3, R^4 = H, alkyl, aryl; R^5 = alkyl, aryl; solvent: Et_2O, THF, 1,4-dioxane, DME, benzene, toluene, MeCN, DMF, DMSO; metal: Zn, Mg, Cd, Ba, In, Ge, Co, Ni, Ce; metal salt: SmI_2, $CrCl_2$, $TiCl_2$, CeX_3, Na_2Te, R_3SnLi, R_3Sb/I_2, Et_2AlCl;

Mechanism:



zinc enolate
(Reformatsky reagent)

Aldol reaction.



Synthesis. 2008 (3): 409.

Organometallics.1984, **9** (3): 1403.

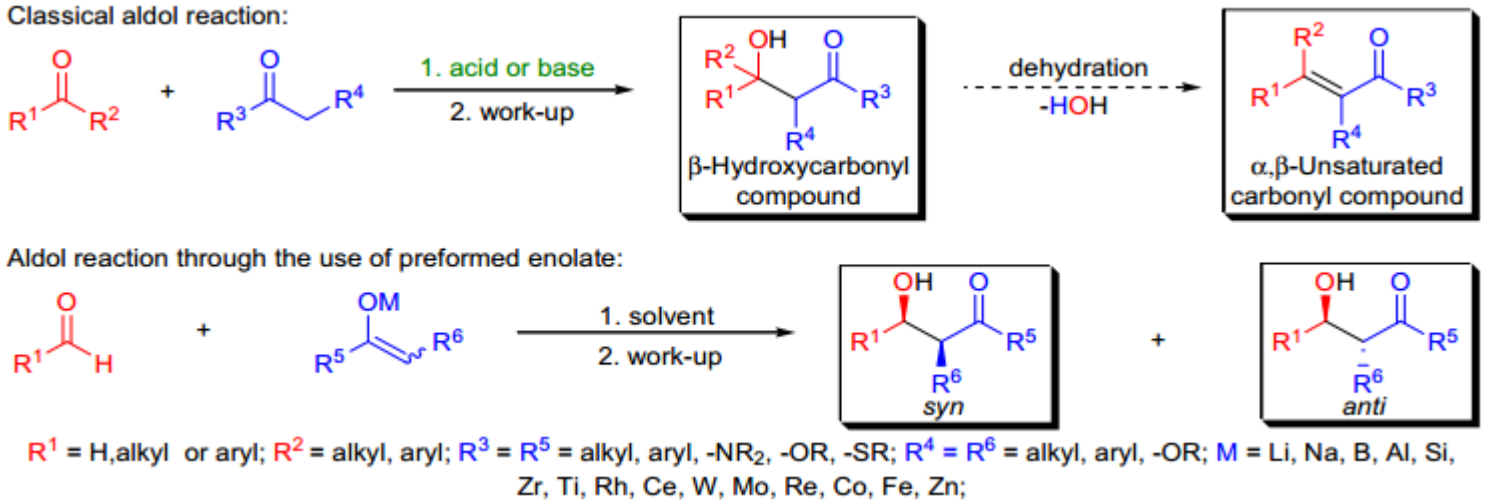
The general features of the Reformatsky reaction

- 1) the reaction is most commonly carried out in a single step by addition of the α-halo ester and the carbonyl compound to the suspension of the activated zinc, but preforming the organozinc reagent prior to the addition of the electrophile is also possible;
- 2) most often ether solvents are used such as Et_2O, THF, 1,4-dioxane and DME, but mixtures of these solvents with aromatic hydrocarbons and more polar solvents such as MeCN, DMF, DMSO, and HMPA are also used;
- 3) organozinc reagents can be formed from 2-bromoalkanoates, α-bromo ketones, alkyl 2-bromomethyl-2-alkenoates, and alkyl 4-bromo-2-alkenoates;
- 4) in addition to aldehydes and ketones, Reformatsky reagents also react with esters, acid chlorides, epoxides, nitrones, aziridines, imines, and nitriles (Blaise reaction).

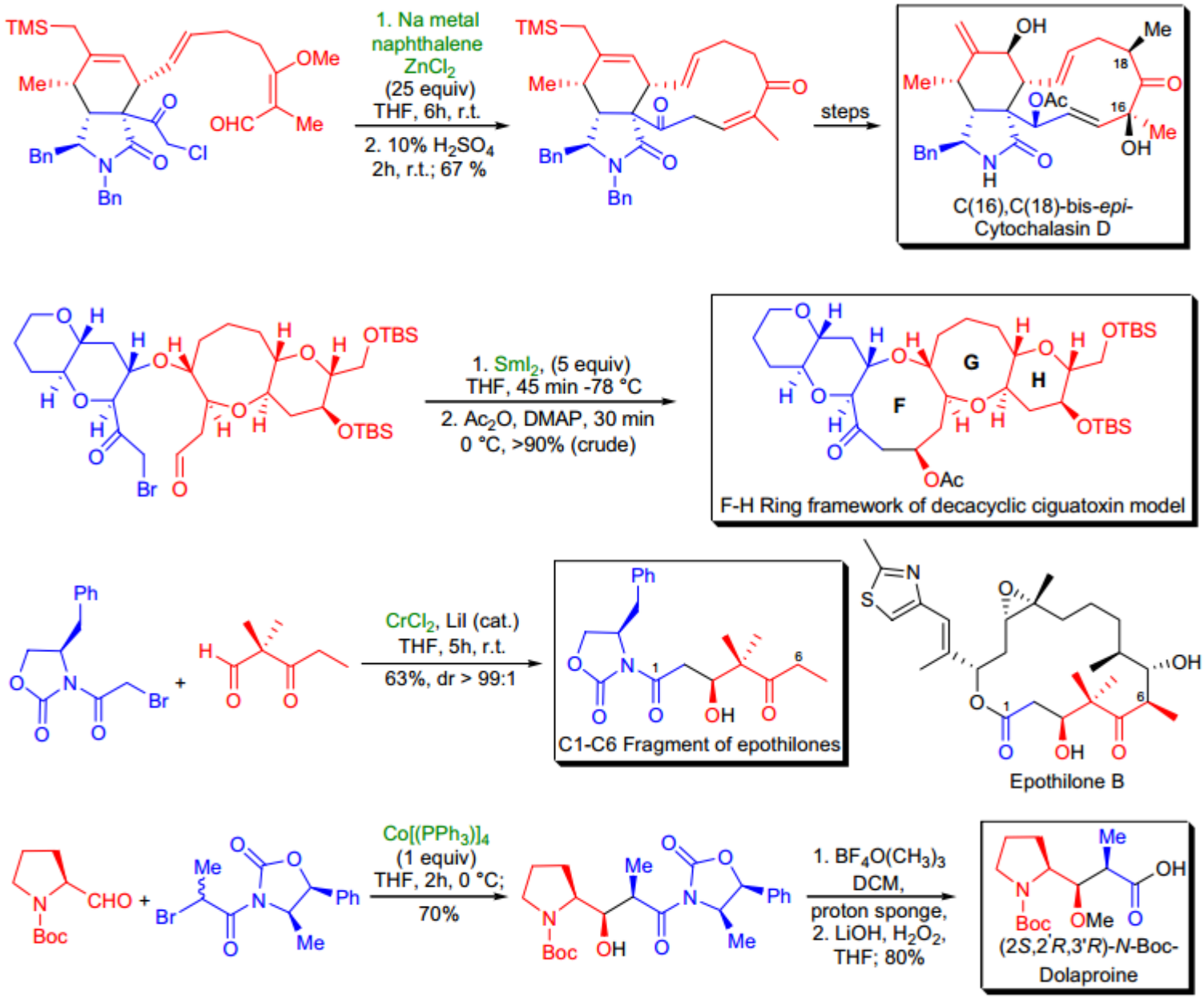
- The scope of the Reformatsky reaction was considerably extended by the development zinc-activation procedures.
- Activated zinc metal can be formed in two ways:
- 1) by removal of the deactivating zinc oxide layer from the metal surface employing reagents such as iodine, 1,2-dibromoethane, copper(I) halides, mercuric halides or by using zinc-copper or zinc-silver couple;
- 2) by reduction of zinc halides in solution by various reducing agents such as potassium (Rieke zinc), sodium- or lithium naphthalide and potassium-graphite laminate (C8K) to form finely dispersed zinc metal. Metals other than zinc were also used including Li, Mg, Cd, Ba, In, Ge, Co, Ni, Ce.

- A major breakthrough in the Reformatsky reaction was the application of metal salts with favorable reduction potentials
- the most important ones being SmI_2, $CrCl_2$, $TiCl_2$. These reactions often can be carried out under mild conditions and afford the products with high stereoselectivity.
- In addition to these metal salts, CeX_3, Na_2Te, R_3SnLi, R_3Sb/I_2, Et_2AlCl can also be employed.

- The main advantages of the Reformatsky reaction over the classical aldol reaction are the following:
- 1)the reaction succeeds even with highly substituted ketone substrates;
- 2) the ester enolate can be formed in the presence of highly enolizable aldehyde and ketone functionalities;
- 3) the reaction is uniquely suited for intramolecular reactions.



Synthetic Applications:



Thanks