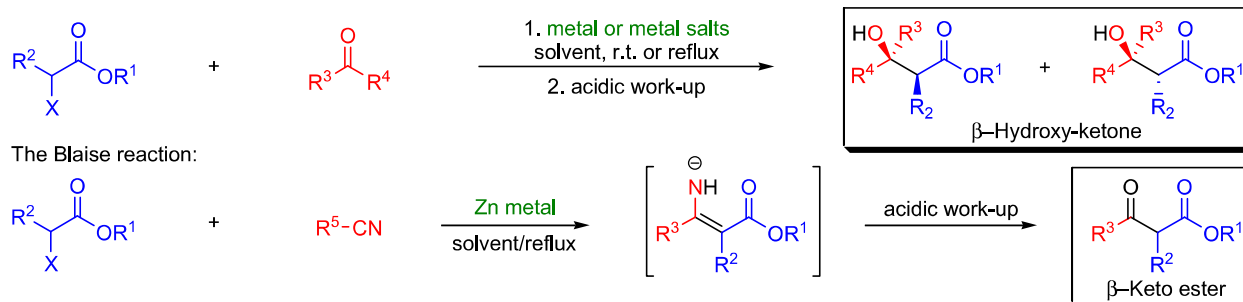


REFORMATSKY REACTION

(References are on page 661)

Importance:[Seminal Publication¹; Reviews²⁻¹⁹; Modifications & Improvements²⁰⁻³⁷; Theoretical Studies³⁸⁻⁴⁰]

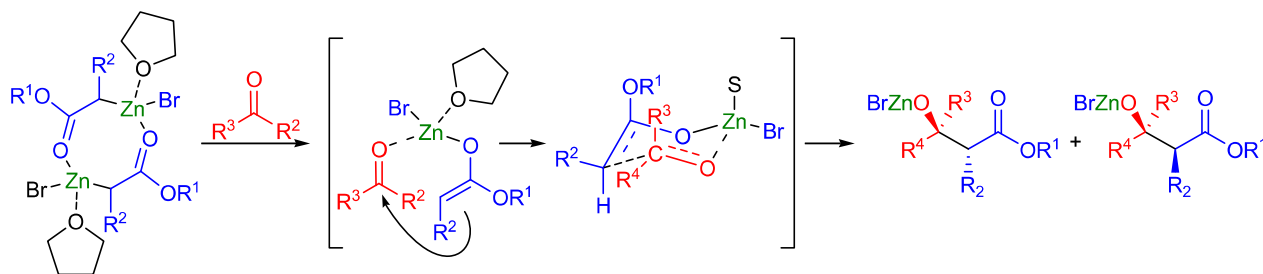
In 1887, S. Reformatsky, reported that in the presence of zinc metal, iodoacetic acid ethyl ester reacted with acetone to yield 3-hydroxy-3-methylbutyric acid ethyl ester.¹ Since this initial report, the classical *Reformatsky reaction* was defined as the zinc-induced reaction between an α -halo ester and an aldehyde or ketone. The scope of the reaction, however, extends far beyond this original definition, and today, the metal-induced reaction of α -carbonyl halides with a wide range of electrophiles are referred to as the *Reformatsky reaction*. The reaction is a two stage process: first the activated zinc metal inserts into the carbon-halogen bond, and this is followed by the reaction of the zinc enolate (Reformatsky reagent) with the carbonyl compound in an *aldol reaction*. The general features of the *Reformatsky reaction* are:^{5,7,9} 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 performing the organozinc reagent prior to the addition of the electrophile is also possible; 2) most often ether solvents are used such as diethyl ether, tetrahydrofuran, 1,4-dioxane and dimethoxyethane, but mixtures of these solvents with aromatic hydrocarbons and more polar solvents such as acetonitrile, dimethyl formamide, dimethyl sulphoxide, and hexamethylphosphoric triamide are also used; 3) organozinc reagents can be formed from 2-bromoalkanoates, α -bromo ketones, alkyl 2-bromomethyl-2-alkenoates,⁴¹ and alkyl 4-bromo-2-alkenoates⁴²; and 4) in addition to aldehydes and ketones, *Reformatsky reagents* also react with esters,⁴³ acid chlorides,⁴⁴ epoxides,⁴³ nitrones,⁴⁵ aziridines,⁴⁶ imines,⁴⁷ and nitriles⁴⁸ (*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:⁷ 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;^{2,5,7,9,12} and 2) by reduction of zinc halides in solution by various reducing agents such as potassium⁴⁹ (*Rieke zinc*), sodium⁵⁰ or lithium naphthalide⁵¹ and potassium-graphite laminate⁵² (C₈K) to form finely dispersed zinc metal. Metals other than zinc were also used including lithium,²² magnesium,²⁰ cadmium,²⁸ barium,³⁷ indium,^{21,34} germanium,³⁶ nickel,³¹ cobalt,³⁵ and cerium.²⁴ A major breakthrough in the *Reformatsky reaction* was the application of metal salts with favorable reduction potentials, the most important ones being samarium(II) iodide,^{23,32,33} chromium(II) chloride,²⁹ and titanium(II) chloride.²⁵ These reactions often can be carried out under mild conditions and afford the products with high stereoselectivity. In addition to these metal salts, cerium(III) halides,³⁰ disodium telluride,³⁰ trialkylantimony/iodine,^{26,27} and diethylaluminum chloride^{26,27} 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; and 3) the reaction is uniquely suited for intramolecular reactions.



X = Cl, Br, I; R¹ = alkyl; R² = H, alkyl, aryl; R³, R⁴ = H, alkyl, aryl; R⁵ = alkyl, aryl; solvent: Et₂O, THF, 1,4-dioxane, DME, benzene, toluene, MeCN, DMF, DMSO; metal: Zn, Mg, Cd, Ba, In, Ge, Co, Ni, Ce; metal salt: SmI₂, CrCl₂, TiCl₂, CeX₃, Na₂Te, R₃SnLi, R₃Sb/I₂, Et₂AlCl;

Mechanism: ⁵³⁻⁵⁷

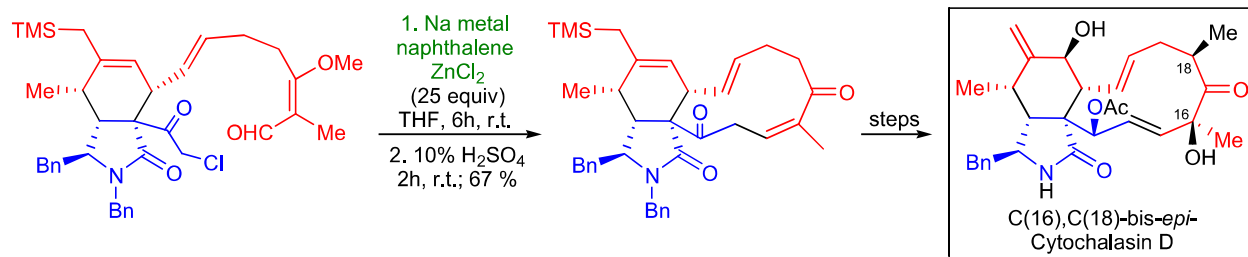
Spectroscopic^{53,56} and crystallographic^{54,55} studies of Reformatsky reagents derived from α -halo esters showed that the enolate is present in the C-enolate form and in ether solvents they form dimers. Enolates derived from α -halo ketones prefer the O-metal enolate form.⁵⁷ It is assumed, based on theoretical calculation,³⁸ that the zinc enolate dimers are dissociated by the action of the carbonyl compound and converted to the corresponding O-zinc enolates. Subsequently, the reaction goes through six-membered chairlike transition state.



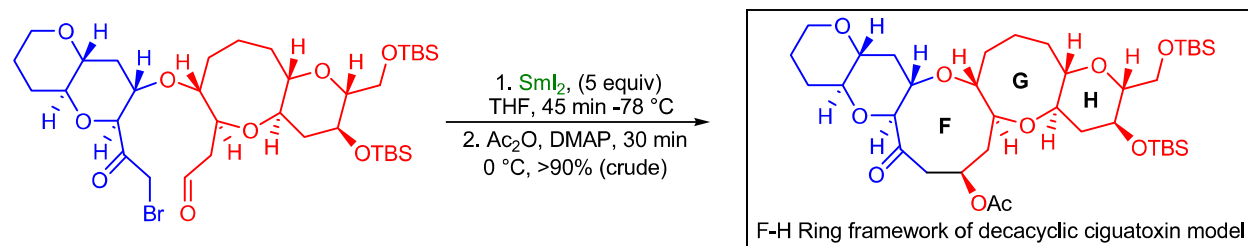
REFORMATSKY REACTION

Synthetic Applications:

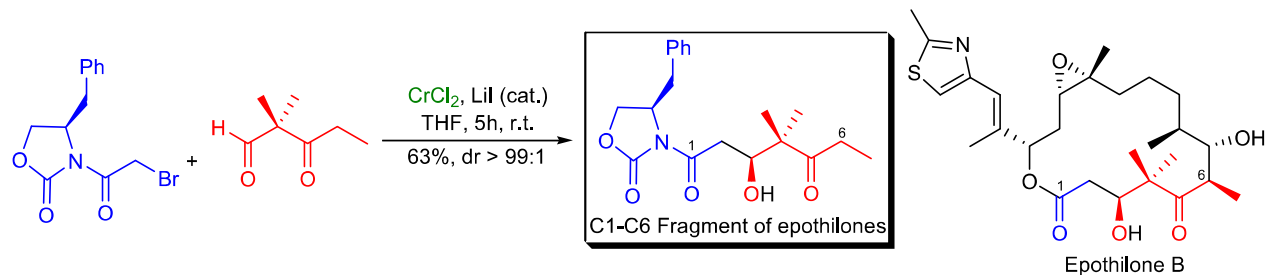
Cytochalasins are macrocyclic natural products possessing a broad range of biological activity. During the synthesis of **C16, C18-bis-*epi*-cytochalasin D**, E. Vedejs and co-workers utilized the *Reformatsky reaction* to close the twelve-membered macrocyclic ring.⁵⁸ The reaction was induced by finely dispersed zinc metal, which was formed by the reduction of ZnCl₂ by sodium naphthalene. The cyclization was carried out at room temperature by the slow addition of the substrate to the above metal suspension. To effect full elimination of the hydroxyl group and hydrolyze the methyl enol ether subunit, the product was treated with 10% H₂SO₄ upon work-up. Subsequent steps led to the formation of C(16),C(18)-bis-*epi*-cytochalasin D, the structure of which was proven by spectroscopic methods and X-ray crystallography.



Ciguatoxin and its congeners are naturally occurring polycyclic ethers, which exhibit high affinity binding to voltage-sensitive sodium channels (VSSC). The scarcity of these compounds from natural sources and their structural complexity necessitated the construction of more accessible model systems in order to investigate their interaction with VSSC and conduct structure-activity relationship studies. In the laboratory of M Sakai, a highly convergent synthesis of the **decacyclic ciguatoxin model** containing the F-M ring framework was accomplished.⁵⁹ To construct the fused oxononane ring system, a SmI₂-mediated intramolecular *Reformatsky reaction* was utilized. The reaction was carried out at -78 °C in THF to give the desired oxacyclic ring with high yield and as a single diastereomer. The resulting hydroxyl group was protected *in situ* as an acetate ester.



L. Wessjohn and co-workers successfully applied the CrCl₂-mediated *Reformatsky reaction* for the synthesis of **C1-C6 fragment of epothilones**.⁶⁰ In their approach, they utilized the Evans (*R*)-4-benzyl-oxazolidinone chiral auxiliary to control the absolute stereochemistry. The chromium-*Reformatsky reaction* between the (*R*)-4-benzyl-3-(2-bromoacetyl)-oxazolidinone and 2,2-dimethyl-3-oxo-pentanal occurred with complete chemoselection providing the product with 63% yield and as a single diastereomer.



G.R. Pettit and co-workers used a novel *tetrakis*(triphenylphosphine)cobalt(0)-promoted *Reformatsky reaction* for the synthesis of a dolastatin 10 unit, **dolaproine** in a Boc-protected form.⁶¹

