Encyclopedia of Reagents for Organic Synthesis

Editor-in-Chief

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Volume 4

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West Sussex PO19 1UD, England
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John Wiley & Sons, Inc., 605 Third Avenue,
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Rexdale, Ontario M9W 1L1, Canada

John Wiley & Sons (SEA) Pte Ltd, 37 Jalan Pemimpin #05-04,
Block B, Union Industrial Building, Singapore 2057

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 0 471 93623 5

Chemical structures produced in ChemDraw by Synopsys, Leeds
Data Management and Typesetting by Reed Technology and Information Services, London
Printed and bound in Great Britain by BPC Wheatons, Exeter

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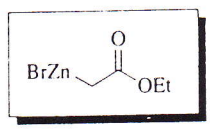
Ethyl Bromozincacetate[1]



[5764-82-9] $C_4H_7BrO_2Zn$ (MW 232.37)

(chemoselective ester enolate reagent[1])

Alternate Name: Reformatsky reagent.

Preparative Methods: see below.

Handling, Storage, and Precautions: α-halo esters and α-halo ketones used for the preparation of Reformatsky reagents are lacrymators and should be used in a well ventilated hood; solutions of the reagent in ethereal solvents are stable at low temperatures for a few days. The reagent is prone to hydrolysis and must be handled in anhydrous solvents under an inert atmosphere.

Introduction. The Reformatsky reagent shown in the above title is the historically first[5] and most widely used zinc ester enolate prepared by zinc insertion into an α-halo ester. However, the Reformatsky reaction can be taken as subsuming all enolate formations by oxidative addition of a metal or a low-valent metal salt into an activated carbon–halogen bond.[1] It is this mode of enolate formation which distinguishes the Reformatsky reaction from other fields of metal–enolate chemistry.

The reagent is dimeric in solution except in the most polar solvents;[2] X-ray analysis of $BrZnCH_2CO_2$-*t*-Bu·THF shows a dimeric unit in the solid state with the metal being bound to an sp^3 carbon atom.[3] In contrast, zinc enolates of ketones are *O*-metalated species.[4]

Performance and Reagent Preparation. Originally,[5] the reaction was performed in a one-step fashion by adding a mixture of the halo ester and the electrophile (usually a carbonyl compound) to a ***Zinc*** suspension in an ethereal or hydrocarbon solvent. However, enolate formation and its reaction with electrophiles can be done successively. This two-step procedure has contributed to the advancement of the Reformatsky reaction, as electrophiles which would quarternize upon mixing with α-halo esters (e.g. azomethines) can be used under these conditions without problems. Moreover, the zinc enolates may be transmetalated prior to use in order to adapt their reactivity to electrophiles beyond the scope of classical Reformatsky reactions.[1]

Difficulties in initiating the reaction are avoided by the use of activated zinc samples.[1a,6] As they promote the reaction even at very low temperatures (Table 1), their use results in generally high yields, the suppression of undesirable side reactions, and an increase in diastereoselectivity. Less reactive donors such as α-chloro esters are equally suited when highly reactive metals are employed.[7] The improved reliability recommends metal-activation techniques for applications to natural product synthesis. Among the zinc samples described so far, finely dispersed and readily prepared zinc/silver on graphite[7] (see also ***Potassium–Graphite***) and zinc obtained by reduction of ***Zinc Chloride*** with ***Potassium Naphthalenide***, ***Lithium Naphthalenide***, or alkali naphthalenides are most effective (Table 1).[8] For large-scale experiments, the application of ultrasound[9] or of electrochemical support[10] for Reformatsky reactions is recommended.

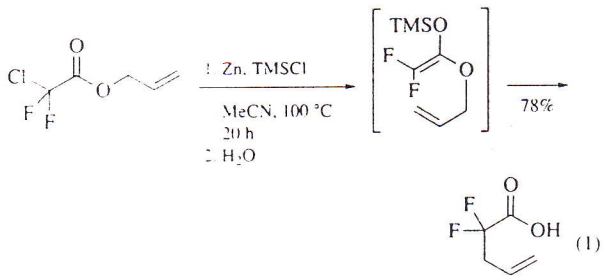
Table 1 Comparison of the Reactivity of Different Zinc Samples for the Preparation of Ethyl Bromozincacetate followed by reaction with Benzaldehyde (A) or Cyclohexanone (B)

Reagent	Carbonyl compound	Solvent	*T* (°C)	*t* (min)	Yield (%)
Zinc dust	A	Benzene	+80	720	61
Zinc dust	B	Benzene	+80	–[a]	56
Zn/Cu couple	A	THF	+66	60	82
Zn/Cu couple	B	THF	+66	60	82
Rieke Zn	A	Et_2O	+25	60	98
Rieke Zn	B	Et_2O	+25	60	95
Zn–ultrasound	A	1,4-Dioxane	+25	5–300	98
$ZnCl_2$/Li[b]	A	Et_2O	0	30	95
$ZnCl_2$/Li[b]	A	Et_2O	–78	30	56
Zn/Ag–graphite	B	THF	–78	20	92

[a] Reaction time not reported. [b] Zinc sample obtained by reduction of $ZnCl_2$ with commercially available lithium dispersion in Et_2O.[8c]

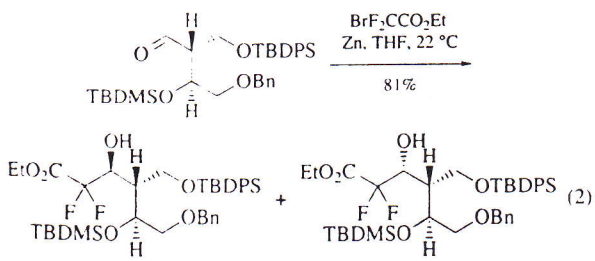
In contrast to other metal enolates, Reformatsky reagents are reasonably stable over a wide temperature range (from –78 °C to above 80 °C for short periods of time) and can be prepared in solvents greatly differing in polarity (most commonly employed are THF, DME, Et_2O, 1,4-dioxane, benzene, toluene, dimethoxymethane, DMF, or mixtures thereof; scattered reports using hexane, acetonitrile, CH_2Cl_2, $B(OMe)_3$, DMSO, and HMPA may be found).[1] The major path for their decomposition is loss of EtOZnBr with formation of ketene which immediately acylates an intact zinc enolate, thus leading to β-keto esters.[11] Reformatsky reagents are therefore usually freshly prepared and used without delay, although solutions of $BrZnCH_2CO_2$-*t*-Bu in a number of solvents were reported to exhibit virtually unchanged reactivity after 4–6 days.[2]

Reformatsky Donors. Ethyl bromoacetate is the most widely used halogen compound for zinc insertion but other short-chain 2-bromo esters work equally well under standard conditions.[1] The alcohol part of the ester plays only a minor role, and by its proper choice (e.g. *t*-butyl, TMS, tetrahydropyranyl bromo esters)[12] β-hydroxy acids can be readily obtained by zinc-induced reaction of these donors with carbonyl compounds followed by hydrolysis of the respective β-hydroxy esters initially formed. Allyl bromo esters on treatment with zinc undergo Claisen rearrangements to 4-alkenoic acids (eq 1).[13] As the chain length of the 2-bromo ester increases, or upon switching to the less reactive 2-chloro ester, the use of highly activated zinc samples and/or more polar solvent systems becomes obligatory in order to accomplish zinc enolate formation.[1]



(1)

Bromo(chloro)difluoro esters and ketones show no peculiarities in their behavior and have found widespread applications in the synthesis of fluorinated natural product analogs (eq 2).[14] In contrast, dibromo-, dichloro-, and trichloroacetates tend to polymerize on reaction with zinc dust at reflux temperatures;[15] however, they can be selectively transformed with more appropriate reagent systems. Depending on the conditions used, they either afford glycidates (with Zn/Ag–graphite at –78 °C)[16] or 2-alkenoates (with Zn/***Diethylaluminum Chloride*** at 0 °C),[17] respectively, on reaction with carbonyl compounds (eq 3).



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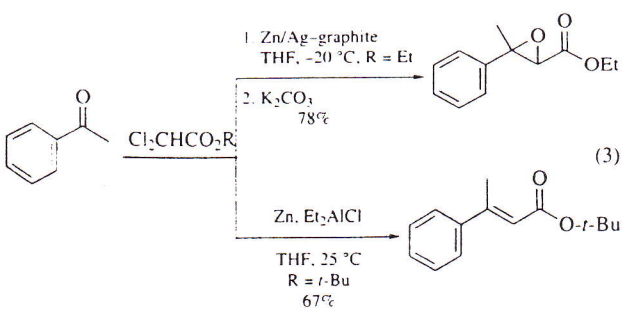
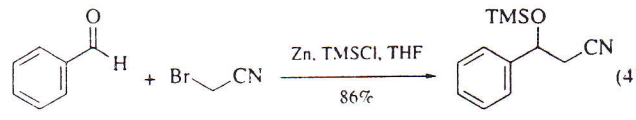


(3)

Haloacetonitriles and α-halo acetamides[1,18] are well suited as donors in Reformatsky reactions (eq 4). When *N*-methoxy-*N*-methylbromoacetamide is used (eq 5), the resulting products may be converted into β-hydroxy ketones by the Weinreb procedure.[19]



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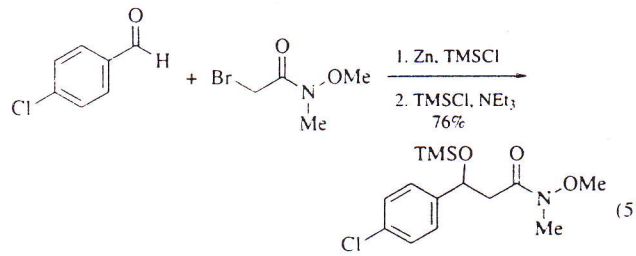
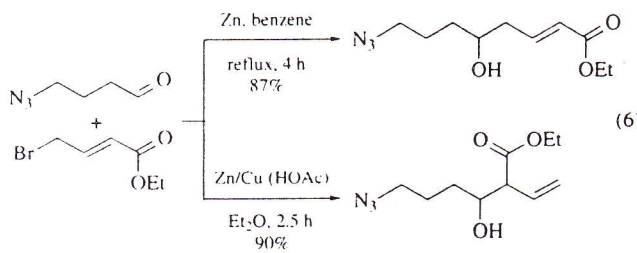


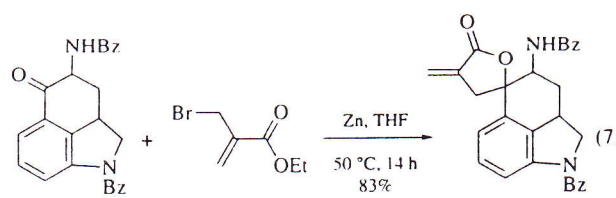
(5)

4-Bromo-2-butenoates as vinylogous bromo esters form ambident carbon nucleophiles upon treatment with zinc, which may either lead to α- or γ-substitution products on reaction with electrophiles. A set of conditions has been worked out that allows control of these pathways, with the polarity of the reaction medium and the temperature being the crucial parameters (eq 6).[20] The data suggest that kinetic control leads to α-products, whereas thermodynamic control affords the γ-substitution products.



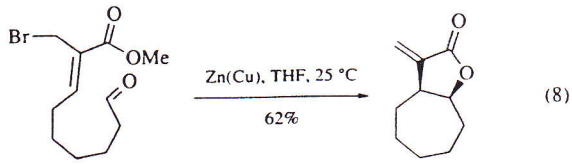
(6)

2-Bromomethyl-2-alkenoates react readily under allylic rearrangement with carbonyl compounds in the presence of zinc to form α-methylene-γ-lactones.[21] Because of the high biological relevance of that structural unit, this reaction has found widespread use in natural product synthesis,[22] both in an inter- (eq 7)[23] and intramolecular fashion (eq 8).[24] With diastereotopic ketones the stereoselectivity of the C–C bond-forming step may be significantly enhanced by using highly reactive Zn/Ag–graphite as promotor at very low temperatures.[25]



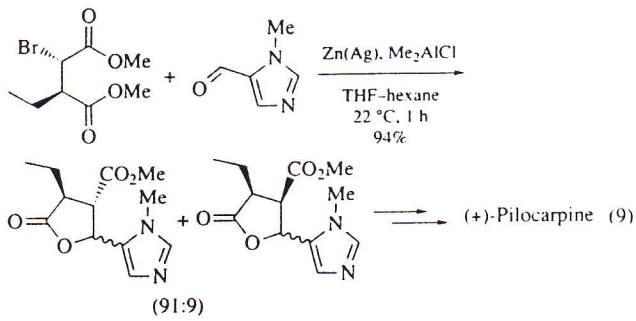
(7)

The particular advantages of the Reformatsky reaction are nicely illustrated by a recent total synthesis of (+)-pilocarpine.[26] Zinc insertion provides a reliable and regioselective access to monoenolates of succinic acid diesters, a difficult task with other methods of enolate formation (eq 9). Although some op-



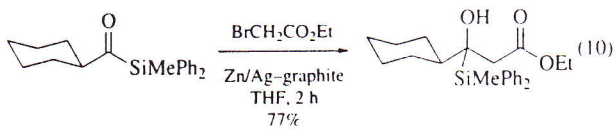
(8)

timization was necessary in order to avoid undesirable side reactions (eliminations), dimethyl (2*S*,3*S*)-2-bromo-3-ethyl-1,4-butandioate could be transformed into the key intermediate of the pilocarpine synthesis in a highly selective manner and in excellent yield.



(9)

Electrophiles. Zinc enolates of esters or ketones show moderate reactivity compared to the respective of alkali metal enolates. Hence, they exhibit higher degrees of chemoselectivity upon treatment with different electrophiles. For a long time, aldehydes and ketones have been the only relevant group of substrates for these reagents and they are still widely used.[1] Examples of Reformatsky reactions with carbonyl compounds of almost any class of natural products can be found in the literature. Highly hindered ketones as well as readily enolizable carbonyl compounds and even acylsilanes (eq 10)[27] are prone to nucleophilic attack. α,β-Unsaturated carbonyl compounds react regioselectively in a 1,2-addition manner with only very few exceptions to this rule. The latter can easily be explained by steric hindrance (eq 11)[4b,28] or peculiar electronic properties of the acceptor molecule, as in aroyl ketene *S,N*-acetals (eq 12)[29] or 1,3-diaza-1,3-butadiene[30] derivatives.



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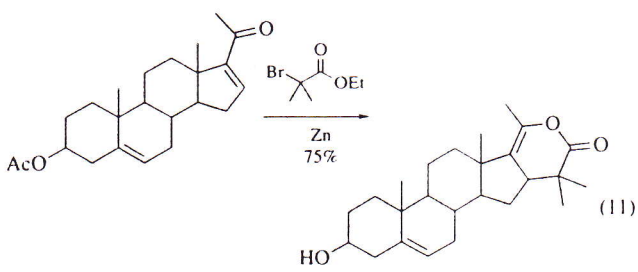
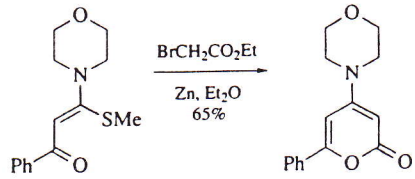


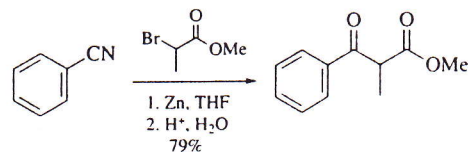
(11)

However, other kinds of electrophiles are also good acceptors for Reformatsky reagents, such as nitriles (sometimes called the



(12)

Blaise reaction) (eq 13),[31,4b] azomethines (preferably via the two-step procedure giving rise to β-lactams) (eq 14),[32] and carboxylic acid chlorides (with assistance of catalytic amounts of Pd^0 complexes) (eq 15).[31c,33] Alkylation of zinc ester enolates, however, is troublesome and restricted to short-chain alkyl iodides, allyl and benzyl halides in aprotic dipolar solvents.[2,34] Under transition metal catalysis they also react with aryl and alkenyl halides or triflates.[35] *C*-Silylation of the zinc enolates by ***Chlorotrimethylsilane*** is essentially confined to bromoacetate (eq 16)[36] and haloacetonitrile.[37]



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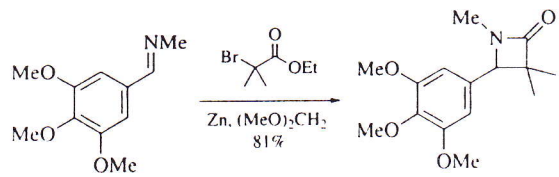

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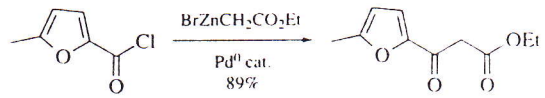

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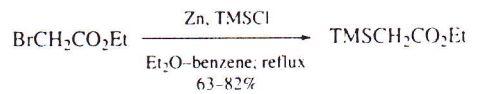
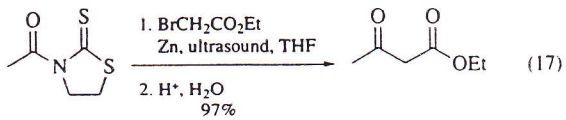
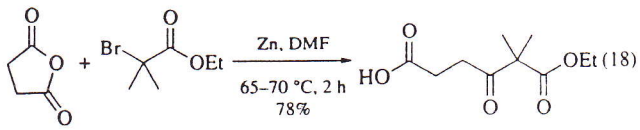


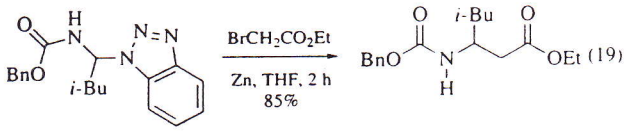
(16)

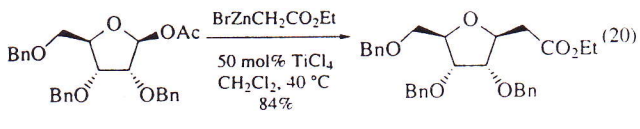
The slightly different reactivity of zinc enolates towards the aforementioned types of electrophiles allows chemoselective transformations of di- or polyfunctional substrates. Although in unsymmetrical diketones no differentiation among the carbonyl groups was reported, keto nitriles, keto amides, keto esters, or halogenated ketones may be attacked exclusively at the carbonyl group.[1]

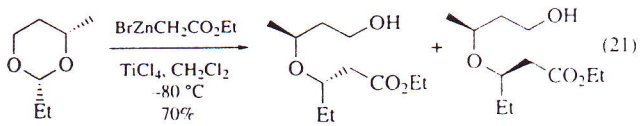
Recent investigations show that 3-acyloxazolidin-2-ones or 3-acylthiazolidine-2-thiones constitute a promising group of acyl donors for zinc enolates (eq 17).[38] Different kinds of anhydrides (eq 18),[39] activated esters, and lactones,[40] including aldonolactones,[41] react smoothly with bromo esters under Reformatsky conditions. Particular emphasis is laid on the high yield of β-amino esters by reaction of zinc enolates with different kinds of *N,O*-acetals and aminals (eq 19).[42] Oxocarbenium cations obtained by in situ activation of acetals with Lewis acids are equally suited as electrophiles in Reformatsky reactions (eqs 20 and 21).[43] A summary of reactions with electrophiles other than carbonyl compounds is given in the literature.[1]





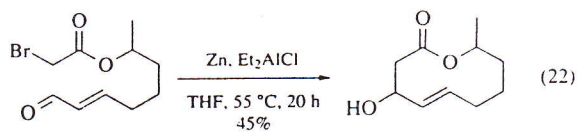


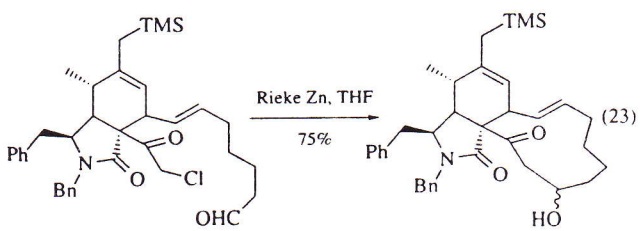




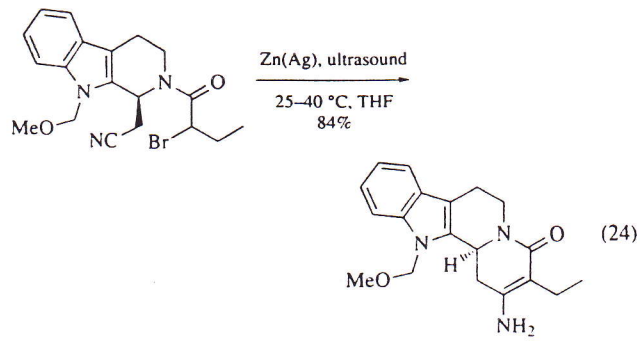
4.2.1

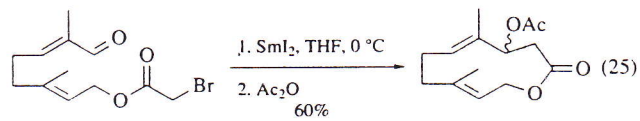
Intramolecular Reformatsky Reactions. As the site of enolate formation is determined by the halogen moiety, Reformatsky reactions are well suited for intramolecular aldolizations. This is a major advantage since regioselective enolate formation by proton abstraction in polycarbonyl systems is a rather difficult task. Thus a homologous series of ω-(α-bromoacetoxy)-aldehydes has been cyclized to β-hydroxy lactones of ring size 13–16,[44] but smaller rings can also be formed in moderate to good yields.[45] This technique has been used in natural product synthesis (eq 22),[46] with the formation of the 11-membered ring of cyctochalasan being the most impressive example (eq 23).[47] Less conventional electrophiles such as nitriles[48] or imides[49] are equally well suited acceptors in entropically favored intramolecular reactions (eq 24).



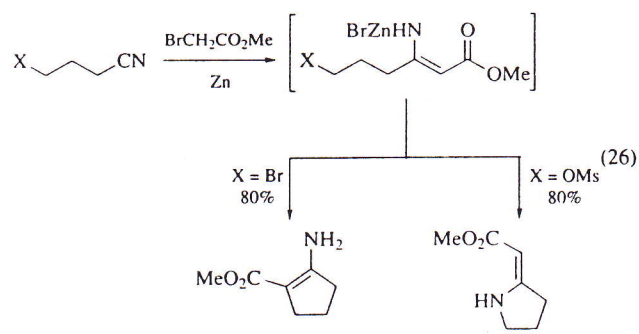


Samarium(II) Iodide as substitute for metallic zinc turned out to be highly advantageous in promoting such cyclizations with formation of normal-, medium-, and large-sized ring systems (eq 25).[50,51] Furthermore, high degrees of diastereocontrol may be exercised via the formation of rigid transition states with the strongly chelating Sm^{3+} counterion.[51]



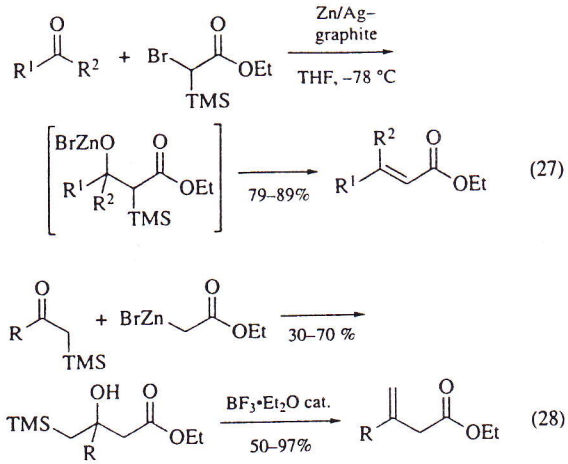


Tandem Reaction. Due to their high tolerance towards different functional groups, zinc enolates are predisposed for reaction sequences. The selective formation of either a carbocyclic or a heterocyclic ring from nitriles bearing an additional halo or sulfonyloxy group within the molecule is an illustrative example of how to impose control on such reaction tandems (eq 26).[52] In this specific case, the hard–soft acid–base (HSAB) principle determines whether the intermediate zinc enamides are *N*-alkylated (X = OSO_2Me) or *C*-alkylated (X = Br). Moreover, *O*-TMS cyanohydrins serve for lactone syntheses in a one-pot procedure.[31c]



Under the rather drastic conditions of conventional Reformatsky reactions (reflux in ethereal or hydrocarbon solvents), the β-hydroxy esters formed may suffer subsequent dehydration in an unselective way. The use of α-silylated Reformatsky donors or of α-silyl ketones shows how to control the regioselectivity of the elimination step.[16,27a] Thus sequences of Reformatsky reactions followed by (in part spontaneous) Peterson eliminations determine the regiochemistry of the newly formed double bond (eqs 27 and 28). When bromo(trimethylsilyl)acetonitrile is used as donor, high to complete (*Z*) selectivity for the α,β-unsaturated nitriles obtained was reported.[53]

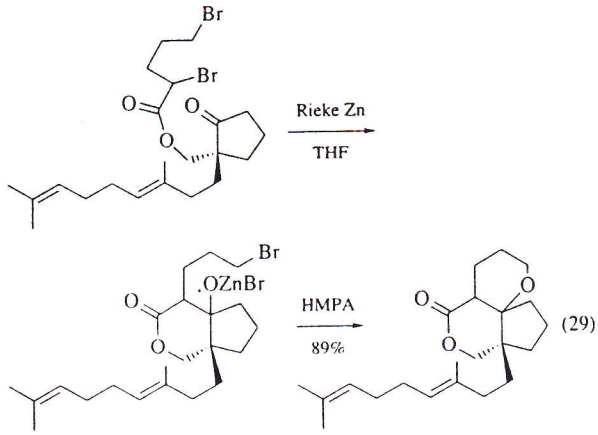
A sequence of an intramolecular Reformatsky reaction with a 2,5-dibromopentanoate donor, followed by etherification of the



(27)

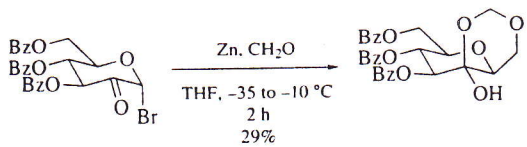
(28)

intermediate zinc aldolate with the terminal bromo group in the presence of HMPA, was ingeniously used to build-up the tricyclic skeleton of daphnilactone and related molecules starting from rather simple precursors (eq 29).[54]



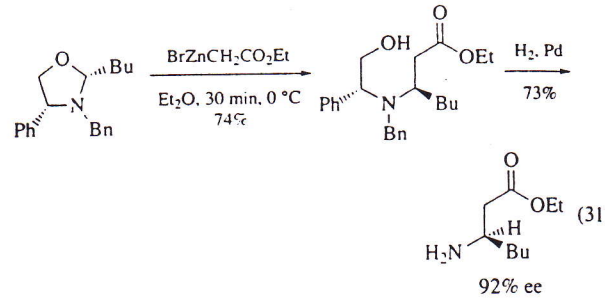
(29)

2-Oxoglycosyl bromides upon treatment with zinc give rise to carbohydrate intermediates with an 'umpoled' anomeric center; the aldolate initially formed on reaction with excess ***Formaldehyde***, together with the residual ketone group on the sugar, trap a second aldehyde molecule with formation of a stable lactol ring (eq 30).[55]



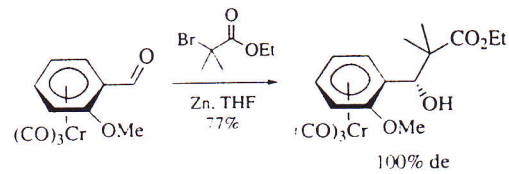
(30)

Stereoselectivity. A general method for highly diastereo- and enantioselective Reformatsky reactions is still missing. Some of the approaches described so far take advantage of the known propensity of zinc(II) to bind to nitrogen donor atoms which may be present in either one of the substrates or in a ligand added to the reaction mixture. With amino carbonyl compounds as electrophiles, for example, highly stereoselective additions are usually observed, and a direct relationship between the complexing ability of the amino group (location, basicity of the N atom) and the de values for the products obtained has been established.[56] A nice illustration of how uncommon electrophiles can be used to prepare enantiomerically enriched products is the ring-opening of enantiomerically pure oxazolidines by zinc ester enolates to β-amino esters, proceeding with inversion of the configuration at the *N,O*-acetal carbon atom (eq 31).[57]



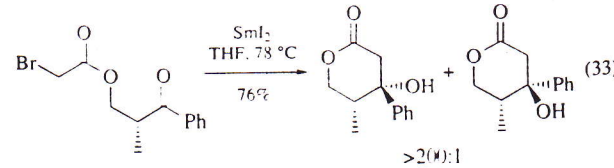
(31)

A means to achieve excellent diastereoselectivity in reactions of *ortho*-substituted benzaldehyde derivatives is the π-face selective attack of a zinc ester enolate on the corresponding tricarbonylchromium complexes (eq 32).[58]

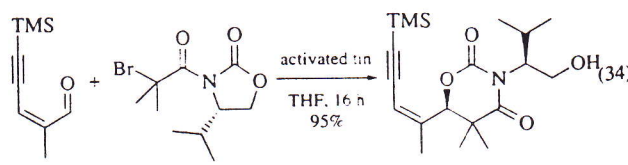


(32)

Preparatively useful degrees of diastereoselectivity have been observed with *N*-(α-bromoacyl)oxazolidinones[59] and/or with metals other than zinc exhibiting higher chelating abilities. For intramolecular reactions, SmI_2 served this purpose very well, because of the rigidity of a Sm^{3+}-chelated bicyclic transition state (eq 33).[51] An Evans-type auxiliary together with activated tin as promotor for the Reformatsky reaction have been employed in a diastereoselective approach to neooxazolomycin (eq 34).[60] With a few exceptions only, induction by chiral alcohol components in α-bromo esters is rather low[61] and until now hardly competitive with today's state of the art in aldol reactions.



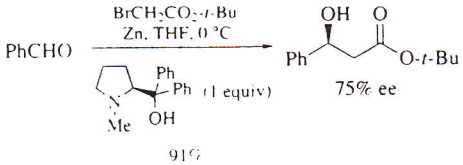
(33)



(34)

In addition to some early reports with (–)-spartein as chiral ligand,[62] promising results of enantioselective zinc- or indium-induced reactions of haloacetates with carbonyl compounds in

the presence of chiral amines or amino alcohols as ligands to the metal have been published recently (eq 35).[63]



(35)

Substitution of Zinc by Other Metals. Oxidative addition into an activated carbon–halogen bond with formation of enolates is by no means restricted to metallic zinc.[1] Low-valent metal salts of adequate reduction potentials such as ***Samarium(II) Iodide***[41d,64,50,51] or ***Chromium(II) Chloride***[65] are equally suited. A great deal of work has been carried out with more or less activated forms of ***Magnesium***,[66] ***Tin***,[67] ***Nickel***,[68] ***Cerium***,[69] ***Indium***,[70] manganese,[71] and cadmium[72] as promotors for Reformatsky-type reactions. Although in specific cases advantages such as increased diastereoselectivity could be drawn from their use, only SmI_2 and to some extent cerium and indium (both are effective with the more reactive α-iodo esters) show reasonable scope. Some representative examples are compiled in Table 2.

Table 2 Reformatsky Reactions with Substitutes for Zinc

Donor	Electrophile	Metal	T(°C)	t(h)	Yield (%)
$BrCH_2CO_2Et$[72]	Cyclohexanone	Cd[a]	35	24	100
ICH_2CO_2Et[70a]	Cyclohexanone	In	20	1.5	65
$BrCH_2CO_2Et$[69]	Benzaldehyde	Ce/Hg	20	17	49
ICH_2CO_2Et[69]	Benzaldehyde	Ce/Hg	0	3.5	81
$BrCH_2CO_2Et$[69]	Acetophenone	Ce/Hg	20	46	60
$BrCH_2CO_2Et$[67]	Benzaldehyde	Sn[b]	25	2	84
$BrCH_2COPh$[67]	Benzaldehyde	Sn	−23	2	63
$BrCH_2CN$[68]	Benzaldehyde	Ni[c]	85	0.7	84
$BrCH(Me)CO_2Et$[64a]	Cyclohexanone	SmI_2	–[d]	–[d]	90
$BrCH_2COPh$[64b]	Benzaldehyde	SmI_2	20	1	75

[a] Rieke Cd. [b] Activated Sn obtained by reduction of $SnCl_2$; only 6% yield with commercial Sn dust in DMF. [c] Rieke Ni. [d] Not reported.

Related Reagents. *t*-Butyl Chloroacetate; *t*-Butyl α-Lithioisobutyrate; Dilithioacetate; Ethyl Lithioacetate; Methyl Bromoacetate; Methyl 4-Bromocrotonate; Methyl Chloroacetate; Potassium–Graphite; Zinc; Zinc/Copper Couple; Zinc–Graphite; Zinc/Silver Couple; Zinc–Zinc Chloride.

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