MICROREVIEW

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Recent Advances on the Catalytic Enantioselective Reformatsky Reaction

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In Memory of Dr. Christian G. Claessens

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This paper reviews the present state of the catalytic enantioselective Reformatsky reaction. Advancements on asymmetric versions of this reaction have recently led to a considerable extension of its scope and applicability, principally due to the use of highly active chiral ligands and very specific reaction conditions.

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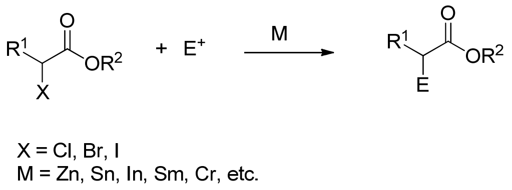
1. Introduction

The classical Reformatsky reaction,[1] introduced for the first time in 1887, consists of the zinc-induced formation of β-hydroxyesters by reaction of α-haloacetates with aldehydes or ketones.[2] Nowadays, a broader definition for the Reformatsky reaction encompasses all those transformations that result from metal insertions into carbon-halogen bonds activated by carbonyl or carbonyl related groups in vicinal or vinylogous positions and subsequent addition to all kind of electrophiles (Scheme 1).



Scheme 1. Reformatsky reaction.

The Reformatsky reaction is amongst the most useful methods for the formation of carbon-carbon bonds. It constitutes an important alternative to the base-induced aldol reaction, with the advantage that no activation by strong acids or bases is needed. The mild reaction conditions required to perform a Reformatsky reaction and therefore, its excellent functional group tolerance, have contributed to its success. Mainly due to its typical heterogeneous character, the principal limitations of the Reformatsky reaction are the lower yields and stereoselectivities in comparison with the aldol reaction, which have often limited its synthetic applications. The development of asymmetric variants of the Reformatsky reaction has also been hampered for its heterogeneous nature. Apart from a few examples with chiral auxiliaries[3] or ligands,[1d,4] no truly catalytic asymmetric version was developed for more than one century since its discovery, when the use of Me_2Zn and Et_2Zn as zinc source allowed the development of homogeneous Reformatsky reactions.[5]

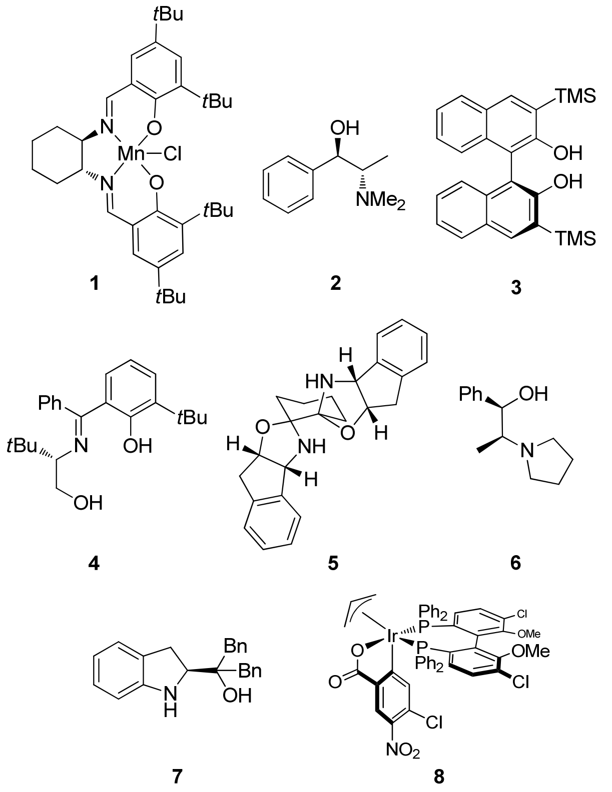


Figure 1. Complexes and ligands employed in the enantioselective Reformatsky reaction.

Considerable research effort has been devoted to identify effective chiral ligands for the catalytic enantioselective

Reformatsky reaction. However, success has been limited to only a few examples. Figure 1 shows the most active and selective ligands employed so far in this transformation. The aim of this minireview is to cover the latest improvements to perform highly enantioselective Reformatsky reactions using these ligands, stressing the essential reaction condition features.

M. Ángeles Fernández-Ibáñez received her Ph.D degree from Universidad Autónoma de Madrid (UAM), Spain, in 2006 under the supervision of Prof. José L. García Ruano. During this period, she had a predoctoral stay in Boston College, USA, with Prof. Scott J. Miller. Subsequently, she joined as a postdoctoral researcher (2006-2009) the group of Prof. Ben. L. Feringa at the University of Groningen, The Netherlands. After one year in the Medicinal Chemistry Institute at CSIC in Madrid, she moved to the group of Prof. Juan Carlos Carretero at the UAM as Research Associate. In 2012 she was appointed Assistant Professor at the Department of Organic Chemistry at the UAM. Her work focuses on asymmetric catalysis and activation of C-H bonds.

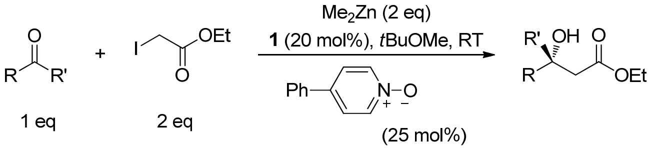
Beatriz Maciá graduated in Chemistry at the University of Alicante (Spain), and obtained her Ph.D in 2005 working in 'Arene Catalyzed Lithiation Processes' with Prof. Miguel Yus at the same University. In 2006 she joined the group of Prof. Ben L. Feringa in Groningen, The Netherlands, as a postdoctoral fellow, where she worked in asymmetric catalysis and molecular nanotechnology. From February 2010 to May 2012, she held an Assistant Professor position in the Department of Organic Chemistry at the University of Alicante where she started her independent research, focused on organic synthesis and asymmetric catalysis. In June 2012, Beatriz Maciá joined the School of Science and the Environment at Manchester Metropolitan University as a Lecturer in Organic Chemistry.

Diego A. Alonso studied chemistry at the University of Alicante obtaining there his B.Sc. and Ph.D. (1997). After a postdoctorate (1997-1999) with Prof. Pher G. Andersson at Uppsala University working on asymmetric catalysis, he returned to Alicante University (1999) as a senior scientist and Ramón y Cajal researcher (2001). In 2003 he became Associate Professor at the same university. He has been visiting scientist at Groningen University with Prof. Ben L. Feringa (2005) and at The Scripps Research Institute with Prof. Carlos F. Barbas, III (2007). He is co-author of nine chapter books and over fifty-five chemistry articles in international journals and he has supervised the research of 5 PhD students. His research interests are focused in organometallic catalysis and asymmetric organocatalysis. He is editor of the journal Asymmetric Organocatalysis and member of the editorial board of the journal International Journal of Chemistry. Currently, he is the Head of the Organic Chemistry Department at the University of Alicante.

Isidro M. Pastor conducted his undergraduate studies at the University of Alicante and graduated in 1996. He undertook Ph.D. studies under the guidance of Prof. Miguel Yus at the same university. After his graduation (Ph.D.) in October 2000, he moved to the Stockholm University for a two-year post-doctoral stay with Prof. Hans Adolfsson. In the beginning of 2003 he moved back to Alicante and started as an assistant professor at the University of Alicante. In 2010, he became Associate Professor at the same university. His research interests are in the field of organolithium reagents, heterocyclic chemistry and organometallic catalysis.

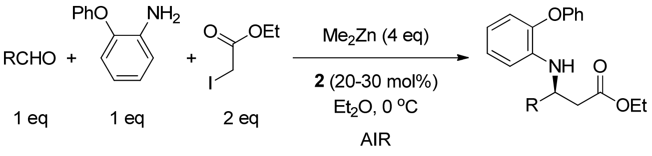
2. Iodo Derivatives in the Reformatsky Reaction

The first example of a catalytic enantioselective Reformatsky reaction, reported by Cozzi in 2006, involves the use of ketones as electrophiles and a chiral [MnCl(salen)] complex as ligand (Scheme 2).[6] The Reformatsky reagent is prepared in situ from ethyl iodoacetate under homogeneous conditions, employing Me_2Zn as a zinc source. The reaction proceeds at room temperature with moderate yields (30-78%) and long reaction times (20-120 h) and the use of 4-phenylpyridine *N*-oxide improves the enantioselectivity of the reaction. Both electron–poor and electron-rich aromatic ketones provide good enantioselectivites (69-86%), while aliphatic substrates provide moderate to low enantioselectivites (23-86%), with the exception of the rigid 2,2-dimethylcyclopentanone, which furnishes the corresponding tertiary alcohol with 96% ee.



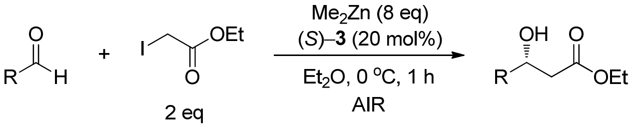
Scheme 2. Dimethylzinc mediated Reformatsky reaction promoted by manganese salen complex **1**.[6]

The same year, Cozzi reported the first and, till date, only catalytic enantioselective imino-Reformatsky reaction described in the literature.[7] The imine is prepared *in situ* by condensation of equimolar amounts of the corresponding aldehyde and *o*-phenoxyaniline, in the presence of Me_2Zn (that acts as dehydrating agent), ethyl iodoacetate and 20-30 mol% of *N*-methylephedrine (**2**), at 0 ºC (Scheme 3). The protocol requires the admission of air into the reaction mixture, in order to obtain reproducible results. Under these reaction conditions, a wide variety of β-aminoesters are obtained in excellent yields (up to 92%) and good levels of enantioselectivities (83-94%).



Scheme 3. One-pot three-component Reformatsky reaction.[7]

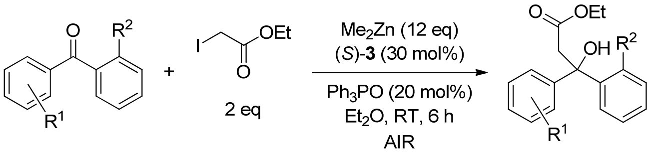
Due to their higher reactivity, a catalytic enantioselective version of the Reformatsky reaction for aldehydes proved to be more challenging, and it was not reported till two years later, by Feringa et al.[8] In Feringa's work, a readily available BINOL-derivative is used as chiral catalyst and the reaction is performed with ethyl iodoacetate as nucleophile and Me_2Zn as the zinc source. Importantly, the presence of air, which initiates a radical mechanism upon reaction with Me_2Zn, is necessary to obtain good conversions. The slow addition of the aldehyde (over 10 min) to the reaction mixture is also required in order to suppress the non-catalyzed reaction. Under these conditions, aromatic aldehydes provide good yields (56-87%) and enantioselectivities (54-84%); whereas aliphatic substrates only reach modest levels of enantioselectivity (30-50%) in bulky systems (*e.g.* isobutyraldehyde, pivaldehyde).



Scheme 4. Reformatsky reaction with aldehydes using BINOL derivative ligand (*S*)-**3**.[8]

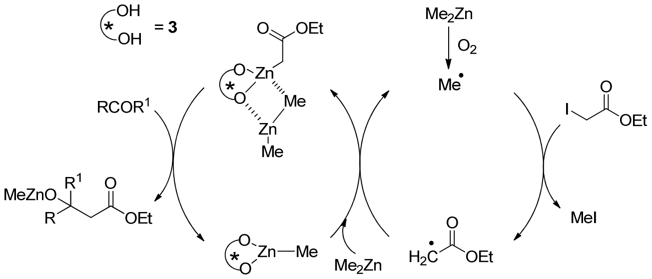
Feringa's catalytic system is equally efficient when applied to ketones, with yields in the range of 60-89% and enantioselectivities from 50-90%.[9] The reaction conditions are analogous to the reaction with aldehydes, with the only difference that the addition of the ketone to the reaction mixture must be slower (over 30 min) and the total amount of Me_2Zn must be added in two portions. The reaction proceeds with good yields (60-85%) and enantioselectivities (50-90%) for aromatic substrates. Aliphatic ketones follow the same trend than the Reformatsky reaction previously reported by Cozzi,[6] and only rigid substrates like 2,2-dimethylcyclopentanone provide the corresponding carbinols with good enantioselectivities.

Importantly, Feringa's catalytic system for Reformatsky reactions constitutes the first example of enantioselective nucleophilic addition of carbon nucleophiles to diaryl ketones.[10] The similarity between two aryl substituents at the ketone functionality, make this kind of substrates very challenging towards an enantioselective nucleophilic addition. The BINOL derivative **3** allows the preparation of chiral diaryl substituted tertiary alcohols with good enantioselectivities (32-91%) and moderate to good yields (33-74%, Scheme 5), using similar conditions as the ones optimized for the reaction with mono-aromatic ketones[9] or aldehydes.[10] In this case, slow addition of the substrate is not necessary, but reactions are performed with higher amount of chiral ligand **3** (30 mol%) and higher excess of Me_2Zn (which must be added in three portions). The use of 20 mol% of Ph_3PO significantly enhances the enantioselectivity of the process. Unfortunately, the reaction has two main limitations: (i) bulky and/or electron-withdrawing *ortho* substituents do not give any conversion and (ii) p*ara*- and *meta*- substituted diarylketones provide racemic carbinols.



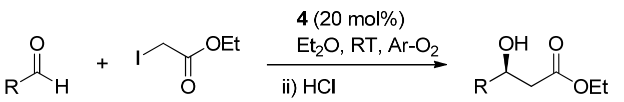
Scheme 5. Reformatsky reaction with *ortho*-substituted diarylketones.[10]

On the basis of the catalytic cycle proposed by Cozzi[7] for the imino-Reformatsky reaction and the zinc intermediates proposed by Noyori,[11] a radical mechanism for the **3**-catalyzed Reformatsky reaction has been proposed (Scheme 6). In the presence of oxygen, Me_2Zn forms alkyl peroxides[12] (ZnOOR) that are able to initiate radical reactions,[13] such as the formation of methyl radical, promoter of the catalytic cycle. Radical trapping experiments have recently verified the existence of this methyl radical.[14]



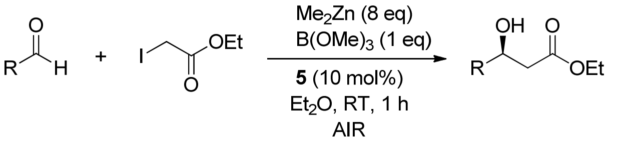
Scheme 6. Proposed catalytic cycle for the Reformatsky reaction promoted by dimethylzinc and air.

Inspired on the pioneer work of Cozzi and Feringa, different catalytic systems based on the formation of radicals from Me_2Zn have been recently described. Hayashi et al. have reported the catalytic enantioselective Refomatsky reaction with aldehydes using Me_2Zn, ethyl iodoacetate and 20 mol% of chiral Schiff base **4** under Ar-O_2 atmosphere (Scheme 7).[15] Under these conditions, good yields (83-99%) and moderate enantioselectivities (30-72%) are obtained for aromatic aldehydes.



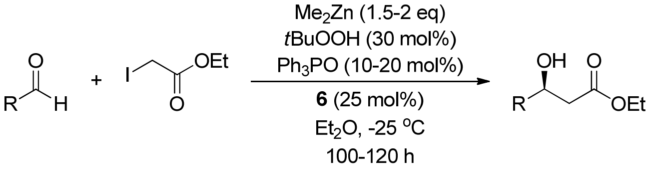
Scheme 7. Reformatsky reaction with aldehydes using chiral Schiff base ligand **4**.[15]

Similarly, Wolf has reported the use of the chiral bisoxazolidine **5** for the Reformatsky reaction with aldehydes, employing ethyl iodoacetate as nucleophile, Me_2Zn as the zinc source and air to promote a radical mechanism (Scheme 8).[16] The reaction proceeds with good enantioselectivities (75-80%) and the use of stoichiometric amounts of trimethoxyborane leads to a 10% increase in the yield of the reaction (final yields of 70-90%). Slow addition of the aldehyde needs to be carried out (over 10 min) and the 8 equiv of Me_2Zn must be added in two portions to achieve good conversions. In contrast to aromatic substrates, relatively low enantioselectivities are obtained with aliphatic aldehydes.



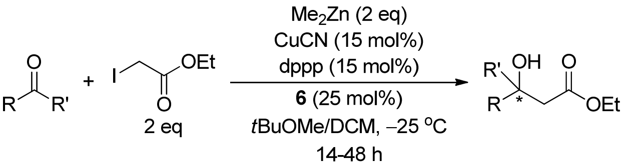
Scheme 8. Reformatsky reaction with aldehydes using bisoxazolidine ligand **5**.[16]

The work of Feringa and Wolf show that the air promoted catalytic enantioselective Reformatsky reaction is very sensitive to unusual parameters. The oxygen has to diffuse into the reaction mixture to initiate the formation of radicals. For this reason, the reaction is dependent on parameters such as the size of the flask, the surface area at the gas-liquid interface, the timing of the exposure to air and the addition sequence of the different reagents. In this context, and in order to gain control over the reaction progress, Cozzi et al. have employed *t*BuOOH instead of oxygen to promote the halogen – zinc exchange.[17] In combination with the inexpensive and commercially available (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol (**6**) as catalyst, this methodology becomes very practical (Scheme 9). The reaction is carried out in the presence of 25 mol% of **6**, and Ph_3PO (20 mol%) was found to accelerate the reaction. The reaction proceeds with good yields (40-90%) and enantioselectivities (43-93%) for aromatic aldehydes and moderate to low enantioselectivities (40-52%) for aliphatic substrates. Compared to the previous air-promoted methodologies,[8,16] lower amounts of Me_2Zn are here required (1.5-2 equiv *vs* >8 equiv), however reaction times are now much longer (>100 h *vs* 1 h).



Scheme 9. *t*-BuOOH-promoted Reformatsky reaction.[17]

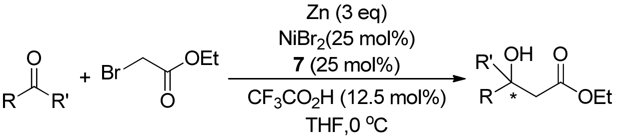
In a similar way, when ketones are used as electrophiles, the Me_2Zn mediated Reformatsky reaction can be alternatively promoted with copper(I) complexes, as recently reported by Cozzi (Scheme 10).[18] The reaction takes place at low temperature (–25 ºC) in the presence of catalytic amounts of *N*-pyrrolidinyl norephedrine (**6**), CuCN and a diphosphine [1,3-bis(diphenyl-phosphino)propane, dppp]. The catalytic system provides high yields (50-90%) and low to moderate enantioselectivities (50-72%) for both aromatic and aliphatic ketones.



Scheme 10. Copper(I)-promoted Reformatsky reaction.[18]

3. Bromo Derivatives in the Reformatsky Reaction

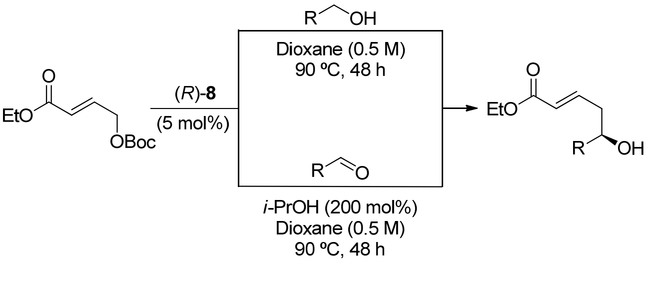
The last development on the heterogeneous catalytic enantioselective Reformatsky reaction with ketones, includes the use of a chiral indolinylmethanol ligand (**7**, 25 mol%) in the presence of $NiBr_2$ (25 mol%), CF_3CO_2H (12.5 mol%) and zinc podwer (3 equiv) (Scheme 11).[19] The reaction proceeds with good yields (52-75%) and enantioselectivities (28-87%) employing ethyl bromoacetate as nucleophile and aromatic ketones as substrates.



Scheme 11. Reformatsky reaction with ketones using indolinylmethanol ligand **7**.[19]

4. Vinylogous Reformatsky Reaction

Last, Krische et al. reported the enantioselective iridium-catalyzed vinylogous Reformatsky reaction using an aldehyde or a primary alcohol, which after dehydrogenation can generate aldehyde-allyliridium pairs (Scheme 12).[20] The reaction takes place with high yields (61-99%), enantioselectivities (83-99%) and linear regioselectivity (from 1:2 to >20:1). This report represents the first example of enantioselective vinylogous Reformatsky-type reaction, and establishes catalytic conditions wherein asymmetric carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level.



Scheme 12. Iridium catalyzed vinylogous Reformatsky reaction.[20]

Conclusions

As it has been summarized in this review, much progress has been made on the catalytic asymmetric Reformatsky reaction over the last 5 years. However, the reaction has not been exploited to its full potential and there is still plenty of room for major improvement regarding yields, enantioselectivities, catalyst loadings and reaction conditions.

Acknowledgments

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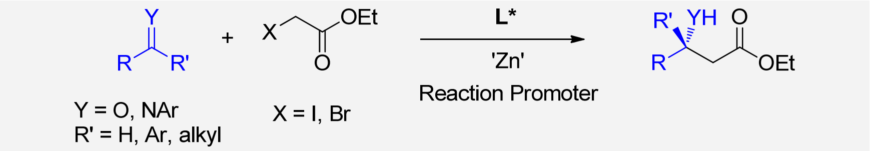
Entry for the Table of Contents

Layout 2:

Reformatsky Reaction



This paper reviews the present state of the catalytic enantioselective Reformatsky reaction. Advancements on asymmetric versions of this reaction have recently led to a considerable extension of its scope and applicability, principally due to the use of highly active chiral ligands and very specific reaction conditions.

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Recent Advances on Catalytic Enantioselective Reformatsky Reaction

Keywords: Enantioselective / Catalysis / Organozinc reagent / Reformatsky reaction / Chiral ligand