Classical Reactions

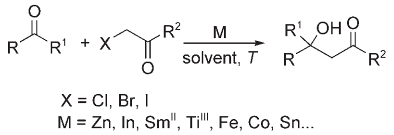
DOI: 10.1002/anie.200604344

Reformatsky Reactions Meet Catalysis and Stereoselectivity**

*Pier Giorgio Cozzi**

Keywords:
catalysis · redox chemistry · Reformatsky reaction · synthetic methods · zinc

The classical Reformatsky reaction[1] was introduced over 115 years ago and consists of the zinc-induced formation of β-hydroxyalkanoates from α-halocarbonyl compounds with aldehydes and ketones. The reaction is initiated by the insertion of zinc into the halogen–carbon bond, and considerable efforts have been made to facilitate this insertion process through activation of the zinc species or the use of other metals in low oxidation states (for example, Sm, Ti, Co, and In; Scheme 1). The reaction is typically heterogeneous, and milder reaction conditions have been developed using activated zinc species (Rieke–Zn[2] and the Cu–Zn couple[3]). The mild reaction conditions and the use of cheap nontoxic metals has attracted synthetic chemists and prompted the development of stereoselective variants. However, the usual heterogeneous reaction conditions have made the development of these variants quite difficult, especially when chiral ligands or promoters are used. In recent years, several new concepts have been introduced that make it possible to reach this goal.



Scheme 1. The Reformatsky reaction.

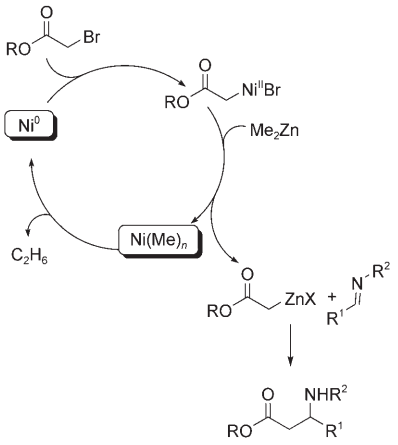
The Reformatsky reaction is a redox processes, and a catalytic redox cycle needs to be designed to develop a catalytic version of the reaction. Catalytic redox cycles have been successfully developed by Fürstner et al.,[4] and enantioselective transformations mediated by titanium[5] and chromium[6] that are based on a redox cycle have now reached a high level of enantiomeric excess. Thus, a catalytic Reformatsky reaction based on chromium appears feasible,[7] and catalytic redox cycles based on iron[8] and samarium[9] have recently been reported. On the other hand, to simplify the design of a catalytic enantioselective transformation, the reaction could be made homogeneous. In this context, homogeneous Reformatsky reactions, in which Me_2Zn or Et_2Zn were used, have recently been reported. Honda and co-workers[10] suggested the use of the Wilkinson catalyst $[Rh(PPh_3)_3Cl]$ in the presence of Et_2Zn as the zinc source, whereas Adrian and Snapper[11] discovered that either $[Ni(acac)_2]$ (acac = acetylacetonate) in the presence of phosphines or $[Ni(PPh_3)_2Cl_2]$ could effectively replace the more expensive Wilkinson catalyst. They also suggested the use of the less nucleophilic Me_2Zn as the zinc source because of its lower reactivity compared to Et_2Zn, and thus no by-products resulting from the transfer of alkyl groups to the electrophile are produced. Another concept developed by Adrian and Snapper, which involved a one-pot, three-component Reformatsky reaction with imines,[11] used a chelating imine derived from *o*-methoxyaniline to direct the Reformatsky reaction to give the β-amino ester. The protecting group on the *o*-methoxyaniline could be removed by oxidative cleavage,[12] although a more general and high-yielding procedure has yet to be developed. The one-pot reaction conditions and the use of a chelating imine were key concepts for the first enantioselective three-component Reformatsky reaction carried out using an excess of *N*-methylephedrine as the chiral ligand.[13] High enantiomeric excesses (up to 92 %) and moderate yields were obtained, and the reaction showed a broad scope. It is worth noting the various tasks that the Me_2Zn species performs in these reactions.

A redox cycle can be proposed for the formation of the zinc enolate in homogeneous Reformatsky reactions (Scheme 2). A key feature of the cycle is the formation of a metal enolate with low reactivity (Rh, Ni) which is unable to react with the carbonyl compounds or with imines. Another important aspect of the homogeneous Reformatsky reaction concerns the possibility of producing successive one-pot transformations in the same reaction flask. For example, Et_2Zn can be used to promote cyclopropanation,[14], and since the homogeneous Reformatsky reaction operates with an excess of Et_2Zn, Cossy and coworkers have achieved a tandem Reformatsky/cyclopropanation reaction with unsaturated acyclic and cyclic ketones.[15]

---

[*] Prof. Dr. P. G. Cozzi
Dipartimento di Chimica "G. Ciamician"
Università di Bologna
Via Selmi, 2 40126 Bologna (Italy)
Fax: (+33) 051-209-9456
E-mail: piergiorgio.cozzi@unibo.it

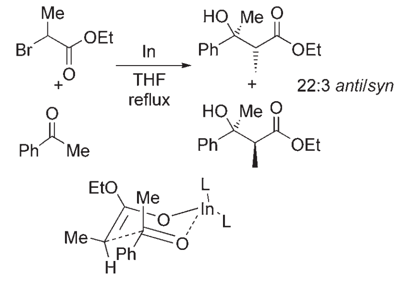
[**] The European Commission through the project FP6-505267-1 (LIGBANK), and PRIN 2005 (Progetto Nazionale: Sintesi e Stereocontrollo di Molecole Organiche per lo Sviluppo di Metodologie Innovative di Interesse Applicativo) are acknowledged for financial support. The Royal Society of Chemistry is acknowledged for a Grant for International Authors. The Hong Kong Polytechnic University (Hong Kong, China) and Prof. A. S. C. Chan are acknowledged for their hospitality.



Scheme 2. Catalytic cycle for a homogeneous imino-Reformatsky reaction.

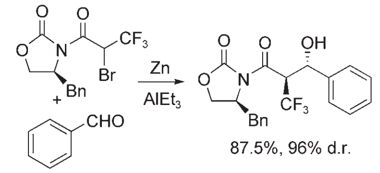
Knochel and co-workers have recently developed a practical, highly enantioselective variant of the Reformatsky reaction, in which a key issue seems to have been the addition of one equivalent of Et_2Zn to the reaction mixture.[16] In other enantioselective variants, two or more equivalents of the Reformatsky reagent are added to a stoichiometric amount of the chiral ligand to form the active metal–zinc complex in situ. The method reported by Knochel and co-workers could prove useful for functionalized enolates, thus increasing the scope of the Reformatsky reaction for the synthesis of natural products. Recently, attractive examples of the use of Reformatsky reagents in total synthesis have been published by several research groups.[17]

Diastereoselective addition of the enolate to ketones is generally problematic because of the reduced reactivity of the enolates and their lower binding affinity to metals. In fact, Reformatsky reactions also generally show low diastereoselectivity on using zinc or other metals. Recently, Baba and co-workers reported an interesting solution to this problem,[18] in which they determined that the Reformatsky reactions mediated by In^I exhibit a distinctive diastereoselectivity with predominant formation of the *anti* product, and they explained the result with a cyclic model (Scheme 3). The addition of indium enolates to chelating ketones may also be controlled by In^{III} or In^I halides, which leads to excellent diastereoselectivity for the *syn* products.



Scheme 3. Diastereoselective Reformatsky reaction mediated by In^0. L = ligand.

Reformatsky reactions are significant when the formation of an unstable enolate is difficult or problematic, for example, with amides or esters containing a CF_3 group in the α-position. Enolates that bear a CF_3 group are practicable in the Reformatsky reaction, and these enolates have been used in stereoselective transformations. Ishihara and co-workers recently showed that the Evans auxiliary can be employed in a Reformatsky-type reaction with aldehydes (Scheme 4).[19] Also, the rhodium-mediated Reformatsky reaction is recommended for the synthesis of difluorocarboxylic esters and difluoro-β-lactams.[20] An interesting observation in these studies was that the selective synthesis of β-lactams or β-amino esters was influenced by the presence of traces of water.[20b]

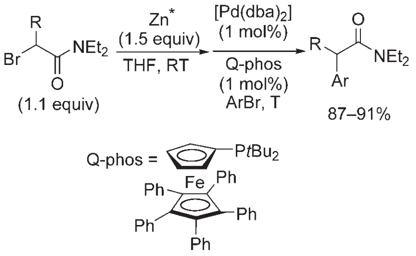


Scheme 4. Reformatsky reaction of 2-bromo-3,3,3-trifluoropropanoic imide in the presence of $AlEt_3$.

Organozinc compounds prepared by halogen–metal exchange are among the most powerful methods for preparing organometallic reagents.[21] Recently, the research group of Knochel disclosed a real breakthrough in this field in that additives can accelerate the exchange reaction.[22] Even highly functionalized zinc reagents can be prepared by exchange reactions with Et_2Zn or with the more reactive $i$$Pr_2Zn$.[23] However, the reactions used undiluted, highly flammable compounds in high excess. It was also found that magnesium salts strongly accelerate these reactions. Eventually, a new procedure for the preparation of alkyl zinc compounds was found, which used direct insertion of the commercially available Zn powder in the presence of LiCl.[24] Translating these observations to the Reformatsky reaction is also possible. The zinc enolate can be prepared by the direct exchange of iodo esters with Et_2Zn[25a] or $i$$Pr_2Zn$.[25b]

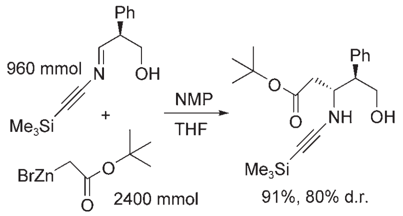
Enantioselective Reformatsky variants based on the exchange between iodoacetate and Et_2Zn have also been developed.[26] A controlled and mild formation of the zinc reagent, in which the less reactive Me_2Zn in the presence of a chiral metal complex was used, produced the first catalytic version of the Reformatsky reaction.[27] The concepts reported involve a homogeneous version of the Reformatsky reaction along with a system able to accelerate the exchange between iodoacetate and Me_2Zn. The exchange reaction was catalyzed by *N*,*N′*-bis(salicylidene)ethylenediamine (salen) ligands, probably through the Lewis basic/Lewis acidic nature of the metal–salen complexes.[28] Among the salen complexes tested, [Mn(salen)Cl][27] emerged as the most effective catalyst. Alternatively, the activation of Me_2Zn seems to be possible by using other concepts. It is well known that Me_2Zn in the presence of oxygen, generates alkyl peroxides (ZnOOR), and these are able to initiate radical reactions.[29] The alkyl peroxide RZnOOR species obtained from the reaction of molecular oxygen with R_2Zn has also been used in enantioselective[30a] and diastereoselective epoxidations.[30b] Zinc enolates can be generated through a radical mechanism, and the catalytic enantioselective addition of these enolates to imines has been carried out.[31] Similarly, Et_3B has been used as a radical initiator, and Lambert and Danishefsky found that a boron enolate can easily be prepared by using an exchange reaction at low temperatures with an iodo derivative in a boron-Reformatsky process.[32]

The α-arylation of a zinc amide and an ester enolate has been reported with enolates generated from the use of Reformatsky conditions.[33] As the basic reaction conditions prevent asymmetric α-arylation, and to overcome the problem related to the α-arylation of amides, Hartwig and co-workers have studied the formation of Reformatsky enolates, both in situ and isolated (Scheme 5).



Scheme 5. Palladium-catalyzed arylation of zinc enolates. dba = *trans*,*trans*-dibenzylideneacetone.

Enolates are important intermediates in the preparation of fine chemicals.[34] However, the use of low temperatures and sensitive enolates are problematic for syntheses performed on a large scale. The Reformatsky reaction, with its convenient one-pot generation of a reactive enolate, appears an attractive solution to difficult synthetic problems in an industrial context. In particular, synthetic procedures for the large-scale preparation of β-amino acids and amino esters have been reported by industrial research groups (Scheme 6).[35]



Scheme 6. A Reformatsky reaction performed on a large scale in industry. NMP = *N*-methyl-2-pyrrolidinone.

To conclude, several new options are now available from modern developments of the Reformatsky reaction, particularly in enantioselective versions. Catalytic, enantioselective, and diastereoselective Reformatsky reactions with varied electrophiles now appear quite possible, and a greater understanding of the properties of the zinc enolate reagents[36] will be achieved in the very near future.

---

[1] a) S. Reformatsky, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210–1212; for recent reviews, see: b) R. Ocampo, W. R. Dolbier, Jr., *Tetrahedron* **2004**, *60*, 9325–9374; c) A. Fürstner, *Synthesis* **1989**, 571–590; d) A. Fürstner in *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**, pp. 287–305; e) J. A. Marshall, *Chemtracts* **2000**, *13*, 705–707; f) J. Podlech, T. C. Maier, *Synthesis* **2003**, 633–655; g) F. Orsini, G. Sello, *Curr. Org. Synth.* **2004**, *1*, 111–135.

[2] For use of Rieke–Zn, see: R. D. Rieke, S. J. Uhm, *Synthesis* **1975**, 452–453.

[3] For use of the Zn–Cu couple, see: E. Santaniello, A. Manzocchi, *Synthesis* **1977**, 698–699.

[4] a) A. Fürstner, A. Hupperts, *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475; b) A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.

[5] a) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

[6] a) G. Xia, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555; b) K. Namba, Y. Kishi, *J. Am. Chem. Soc.* **2005**, *127*, 15382–15383; c) M. Inoue, T. Suzuki, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141; d) A. Berkessel, D. Menche, C. A. Sklorz, M. Schröder, I. Paterson, *Angew. Chem.* **2003**, *115*, 1062–1065; *Angew. Chem. Int. Ed.* **2003**, *42*, 1032–1035; e) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem.* **1999**, *111*, 3558–3561; *Angew. Chem. Int. Ed.* **1999**, *38*, 3357–3359.

[7] L. Wessjohann, T. Gabriel, *J. Org. Chem.* **1997**, *62*, 3772–3774.

[8] M. Durandetti, J. Perichon, *Synthesis* **2006**, 1542–1548.

[9] F. Orsini, E. M. Lucci, *Tetrahedron Lett.* **2005**, *46*, 1909–1911.

[10] a) K. Kanai, H. Wakabayashi, T. Honda, *Org. Lett.* **2000**, *2*, 2549–2551; b) K. Kanai, H. Wakabayashi, T. Honda, *Heterocycles* **2002**, *58*, 47–51.

[11] J. C. Adrian, Jr., M. L. Snapper, *J. Org. Chem.* **2003**, *68*, 2143–2150.

[12] L. C. Akullian, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4376–4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4244–4247.

[13] P. G. Cozzi, E. Rivalta, *Angew. Chem.* **2005**, *117*, 3666–3669; *Angew. Chem. Int. Ed.* **2005**, *44*, 3600–3603.

[14] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53–58.

[15] M.-F. La Roche, D. Belotti, J. Cossy, *Org. Lett.* **2005**, *7*, 171–173.

[16] R. J. Kloetzing, T. Thaler, P. Knochel, *Org. Lett.* **2006**, *8*, 1125–1128.

[17] a) G. Matsuo, K. Kawamura, N. Hori, H. Matsukura, T. Nakata, *J. Am. Chem. Soc.* **2004**, *126*, 14374–14376; b) T. Nagamitsu, D. Takano, T. Fukuda, K. Otoguro, I. Kuwajima, Y. Harigaya, S. Omura, *Org. Lett.* **2004**, *6*, 1865–1867; c) H. Kigoshi, M. Kita, S. Ogawa, M. Itoh, D. Uemura, *Org. Lett.* **2003**, *5*, 957–960; d) P. P. Reddy, K.-F. Yen, B.-J. Uang, *J. Org. Chem.* **2002**, *67*, 1034–1035; e) G. R. Pettit, M. P. Grealish, *J. Org. Chem.* **2001**, *66*, 8640–8642.

[18] a) S. A. Babu, M. Yasuda, Y. Okabe, I. Shibata, A. Baba, *Org. Lett.* **2006**, *8*, 3029–3032; b) S. A. Babu, M. Yasuda, I. Shibata, A. Baba, *J. Org. Chem.* **2005**, *70*, 10408–10419.

[19] T. Shimada, M. Yoshioka, T. Konno, T. Ishihara, *Org. Lett.* **2006**, *8*, 1129–1131.

[20] a) A. Otaka, J. Watanabe, A. Yukimasa, Y. Sasaki, H. Watanabe, T. Kinoshita, S. Oishi, H. Tamamura, N. Fujii, *J. Org. Chem.* **2004**, *69*, 1634–1645; b) K. Sato, A. Tarui, S. Matsuda, M. Omote, A. Ondo, I. Kumadaki, *Tetrahedron Lett.* **2005**, *46*, 7679–7681.

[21] A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 5743–5753.

[22] a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.* **2006**, *118*, 3024–3027; *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem.* **2005**, *117*, 165–169; *Angew. Chem. Int. Ed.* **2005**, *44*, 159–162; c) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336.

[23] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.* **2004**, *116*, 1032–1036; *Angew. Chem. Int. Ed.* **2004**, *43*, 1017–1021.

[24] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186–6190; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

[25] a) K. Maruoka, N. Hirayama, H. Yamamoto, *Polyhedron* **1990**, *9*, 223–226; b) I. Sato, Y. Takizawa, K. Soai, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2825–2826.

[26] Y. Ukaji, S. Takenaka, Y. Horita, K. Inomata, *Chem. Lett.* **2001**, 254–255.

[27] P. G. Cozzi, *Angew. Chem.* **2006**, *118*, 3017–3020; *Angew. Chem. Int. Ed.* **2006**, *45*, 2951–2954.

[28] a) T. Katsuki, *Chem. Soc. Rev.* **2004**, *33*, 437–444; b) P. G. Cozzi, *Chem. Soc. Rev.* **2004**, *33*, 410–421.

[29] J. Lewìnski, W. Śliwiński, M. Dranka, I. Justiniak, J. Lipkowski, *Angew. Chem.* **2006**, *118*, 4944–4947; *Angew. Chem. Int. Ed.* **2006**, *45*, 4826–4829.

[30] a) D. Enders, J. Zhu, G. Raabe, *Angew. Chem.* **1996**, *108*, 1827–1829; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725–1728; b) A. E. Lurain, A. Maestri, A. R. Kelly, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 13608–13609.

[31] P. G. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 2075 – 2079.

[32] T. H. Lambert, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 426 – 427.

[33] T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976 – 4985.

[34] V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734 – 2793.

[35] a) K. Sorger, H. Petersen, J. Stohrer, EP 1394140, **2004**; b) A. K. Awasthi, M. L. Boys, K. J. Cain-Janicki, P.-J. Colson, W. W. Doubleday, J. E. Duran, P. N. Farid, *J. Org. Chem.* **2005**, *70*, 5387 – 5397; c) B. De Lange, H. L. M. Elsenberg, Q. B. Broxterman, M. van der Sluis, P. G. H. Uiterweerd, WO 2006069798, **2006**.

[36] M. L. Hlavinka, J. R. Hagadorn, *Organometallics* **2006**, *25*, 3501 – 3507.

The definitive work in electrochemistry

Encyclopedia of Electrochemistry

Available Volumes:
1: Thermodynamics and Electrified Interfaces
2: Interfacial Kinetics and Mass Transport
3: Instrumentation and Electroanalytical Chemistry
4: Corrosion and Oxide Films
5: Electrochemical Engineering
6: Semiconductor Electrodes and Photoelectrochemistry
7A+7B: Inorganic Electrochemistry
8: Organic Electrochemistry
9: Bioelectrochemistry
10: Modified Electrodes
11: Index

Now complete!

Editors-in-Chief: **Allen J. Bard,** *Department of Chemistry, University of Texas, Austin, USA*/ **Martin Stratmann,** *Max-Planck-Institute for Iron Research, Duesseldorf, Germany*

Stay up-to-date in electrochemistry
- a total of 11 volumes makes this the first and only complete reference on electrochemistry
- covering all aspects, from fundamental research to applications in industry
- easy access to electrochemical topics

www.wiley-vch.de/bard/eoe

2006. 8000 pages with 3000 figures and about 1000 tables. Hardcover.
ISBN 978-3-527-30250-5
€ 299.00*/£ 210.00 per volume. *The €-price is valid for Germany only!

11 volumes (including index volume)

For ordering information, please contact our customer service:

Wiley-VCH
E-Mail: service@wiley-vch.de
www.wiley-vch.de

John Wiley & Sons, Inc.
E-Mail: custserv@wiley.com
www.wiley.com

John Wiley & Sons, Ltd.
E-Mail: cs-books@wiley.co.uk
www.wiley.com

WILEY-VCH

WILEY 1807-2007 KNOWLEDGE FOR GENERATIONS

WILEY InterScience® DISCOVER SOMETHING GREAT

33123702_gu