Practical Chloromanganese–Salen-Catalyzed Enantioselective Reformatsky Reaction with Ketones

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Abstract: The first catalytic enantioselective Reformatsky reaction is realized by a controlled transmetalation of an \( \alpha \)-iodo ester with dimethylzinc in the presence of a chloromanganese–Salen complex (20 mol%) as catalyst and 4-phenylpyridine N-oxide (25 mol%) as additive. The zinc enolate is formed under mild conditions at room temperature; it undergoes enantioselective addition to ketones. The reaction shows broad scope and moderate to good stereoselection and it allows the straightforward preparation of quaternary stereogenic centers.

Key words: Reformatsky reaction, enantioselective, catalysis, chloromanganese–Salen complex, dimethylzinc

Introduction

The classical Reformatsky reaction (Scheme 1),\(^1\) first presented more than 115 years ago, involves the zinc-promoted formation of \( \beta \)-hydroxyalkanoates from \( \alpha \)-halocarbonyl compounds and aldehydes or ketones. Reformatsky reactions are now defined as those resulting from metal insertions into carbon–halogen bonds, activated by carbonyl or carbonyl-related groups in vicinal or vinyllogous positions with a variety of electrophiles. The reaction is initiated by the insertion of zinc into the halogen–carbon bond, and considerable endeavors have been made in order to accelerate the insertion either by the activation of zinc or by the use of other metals (Sm, Ti, Co, In) in low oxidation states. The reaction is typically heterogeneous, and milder conditions have been developed that use activated zinc (Rieke-Zn,\(^2\) Cu–Zn alloy\(^3\)). The Reformatsky reaction has attracted synthetic chemists for its mild conditions and now the focus is on stereoselective variants. However, heterogeneous conditions have made the development of these variants problematic, in particular, the use of chiral ligands or promoters in catalytic amounts. The introduction of new and useful concepts has resulted in the recent introduction of stereoselective variants. The first breakthrough was realized when homogeneous Reformatsky reactions enabled the design of a catalytic enantioselective version. In this context, the homogeneous Reformatsky reaction based on the use of dimethyl- or diethylzinc as a zinc source has recently been reported. Honda\(^4\) reported the use of Wilkinson’s catalyst [RhCl(PPh\(_3\))\(_3\)], in the presence of diethylzinc while Adrian\(^5\) found that inexpensive bis(acetylacetonato)nickel in the presence of phosphines or dichlorobis(triphenylphosphine)nickel could effectively replace the more expensive Wilkinson’s catalyst. Other authors have used these concepts in diastereoselective transformations,\(^6\) while chelating ligands have been used in an enantioselective version.\(^7\) Although an interesting enantioselective nickel-mediated cross-coupling reaction between zinc enolates and bromide has been reported by Fu,\(^8\) attempts to use nickel salts in the presence of a catalytic amount chiral ligand for these homogeneous Reformatsky reactions were unsuccessful.\(^9\)

Recently, Knochel has shown that additives can accelerate the exchange reaction between organometallic reagents and organic halides. The high reactivity of bimetallic intermediates, obtained in a transient form in the presence of inorganic salts, considerably enhances the efficiency of the exchange reaction between the reagents, due to saturation of the organometallic moiety.\(^10\) Higher coordination numbers and more strongly donated ligands dramatically facilitate the formation of ‘ate’ transition states, thus promoting the exchange. Remarkably, bis(acetylacetonato)nickel is able to accelerate the exchange reaction between diethyl- or diisopropylzinc and functionalized organic halides.\(^11\)

Zinc enolates can be prepared by the direct exchange of \( \alpha \)-iodo esters with diethylzinc\(^12\) or diisopropylzinc;\(^13\) this exchange reaction occurs without additives or catalysts.
Clearly, these reagents are too effective for controlled transmetalation accelerated by a catalyst. In fact, the enantioselective addition of zinc enolates, obtained by transmetalation with dimethylzinc to aldehydes and nitriles, was performed only in the presence of a stoichiometric amount of chiral ligand.\textsuperscript{14}

The mild formation of the zinc enolate using less reactive dimethylzinc produced the first catalytic version of the Reformatsky reaction (Scheme 2).\textsuperscript{15} The exchange reaction was performed in the presence of a metal complex able to accelerate the transmetalation. Among the metal complexes and ligands tested, M(Salen) (M = TiCl\textsubscript{2}, VO, AlCl, CrCl) metal complexes were able to accelerate the transmetalation. Among the metal complexes and ligands tested, M(Salen) (M = TiCl\textsubscript{2}, VO, AlCl, CrCl) metal complexes were able to accelerate the exchange reaction. It is worthwhile to mention that, under nitrogen, a mixture of dimethylzinc, acetophenone, and ethyl iodoacetate remains completely unreacted; the acetophenone is recovered after 24 hours at room temperature.

Scheme 2 The catalytic enantioselective chloromanganese–Salen complex Reformatsky reaction.

Although it is still unclear how the Salen ligand was able to act in cooperative manner, and its Lewis basic–Lewis acid nature, probably play a decisive role.\textsuperscript{16} Remarkably, and unexpectedly, a chloromanganese–Salen complex (Scheme 2)\textsuperscript{17} was shown to be the most effective catalyst, with the reaction showing good enantioselectivity with aromatic and hindered aliphatic ketones (Table 1).

Zinc–Salen complex, prepared in situ by mixing the chiral Jacobsen’s Salen ligand\textsuperscript{18} (R,R)-1 with dimethylzinc, was also able to promote the reaction giving, however, the products with lower enantiomeric excess. Several chloromanganese–Salen complexes prepared by the standard methodology described by Jacobsen\textsuperscript{18} were tested in the reaction, without improving the enantiomeric excess.\textsuperscript{15} From these studies it was clear that hindered groups in positions 3 and 3’ of the Salen framework are able to stabilize the chloromanganese–Salen complex towards its reaction with dimethylzinc. In fact, dimethylzinc can react with the chloromanganese–Salen complex in an exchange reaction, producing the less selective zinc–Salen complex.\textsuperscript{19} This feature is well documented in the chemistry of Salen–metal complexes.\textsuperscript{20} This seems to be a limitation in the procedure, as enhancing the stability of the manganese complex towards dimethylzinc or towards the intermediate zinc alkoxides formed during the reaction, would possibly enable the amount of the chloromanganese–Salen complex to be reduced. The mild formation of the zinc enolate allows the use of functionalized and enolizable ketones whose reaction with enolates generated under strong basic conditions would certainly be difficult. Contrary to other Reformatsky reactions, it is not necessary to isolate the Reformatsky reagent; they are sometimes isolated as solid complexes in another reaction flask. The dimethylzinc-mediated Reformatsky reaction seems not to be sensitive to aged dimethylzinc, as old or new dimethylzinc bottle are both effective for promoting the desired transformation. Instead, the enantioselectivity obtained is quite sensitive to the quality of chloromanganese–Salen complex.\textsuperscript{21} Commercially available chloromanganese–Salen complex could be used in this reaction, but commercially available N,N’-bis(3,5-di-tert-butylsalicylidene)-1,2-diaminocyclohexylmanganese(III) chloride (2), both (R,R) or (S,S), from different commercial sources, showed an increased reactivity and a slightly variation minor selectivity compared to the synthesized chloromanganese–Salen complex.

**Scope and Limitations**

A broad variety of ketones were successfully transformed under the reaction conditions, including electron-rich and electron-deficient aromatic, aliphatic, heterocyclic, and \(\alpha,\beta\) unsaturated ketones. Low enantiomeric excess was obtained with aliphatic unbranched ketones. The amount of ligand (R,R)-1 (20 mol%) is still quite high, although the complex (R,R)-2 is easy to prepare in one step, and the ligand (R,R)-1 is commercially available and relatively inexpensive. On the other hand, a different process described for the enantioselective addition of enolates to ketones employs an expensive phosphine, prepared in a multistep reaction sequence.\textsuperscript{22} The conditions described for the chloromanganese–Salen complex (R,R)-2 mediated reaction require a large volume of the solvent (\(t\)-BuOME), and this is certainly a weak point for large-scale applications. We have found that the enantioselectivity of the process is strictly dependent by the high dilution, and low enantiomeric excesses are recorded in more concentrated conditions.

Among all the additives tested, 4-phenylpyridine N-oxide was found important in order to stabilize the chloromanganese–Salen complex (R,R)-2.\textsuperscript{23} The additive slows the reaction considerably (Table 1); times of 40–70 hours are necessary in order to reach moderate conversion with ketones. Unreacted ketone is isolated when the reaction is

\[ \text{Scheme 2} \]

The catalytic enantioselective chloromanganese–Salen complex Reformatsky reaction.
quenched. The inclusion of the additive enhances the enantiomeric excess of the isolated Reformatsky products, when the reaction is performed at room temperature for longer reaction times. The longer reaction times do not produce byproducts derived from the addition of dimethylzinc to the ketone.

As further example for the scope of the process, we report here the addition of ethyl iodoacetate to an aromatic α-halo ketone. This class of substrate is useful for synthetic transformations. The addition of a zinc enolate to an α-bromo ketones would be quite difficult in a classical Reformatsky reaction, as bromo ketones can form zinc enolates when they react in the presence of zinc dust. However, the less reactive α-chloro ketone has been used in a direct Reformatsky reaction. The chemoselectivity of our process is well exemplify by the reaction presented in Scheme 3. Ethyl iodoacetate is selectively transformed into its enolate in the presence of the highly reactive 2-bromoacetophenone (3), in the chloromanganese–Salen complex (R,R)-2 mediated process. Unfortunately, the enantiomeric excess of the product was only modest because of the similar hindrance of the flanking group bearing the bromo substituent compared to the phenyl substituent, and it is also determined by the increased reactivity of the α-bromo ketones. In fact, performing the re-

Table 1  Dimethylzinc-Mediated Enantioselective Reformatsky Reaction with Ketones

<table>
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<tr>
<th>Entry</th>
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<td>24</td>
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<td>77</td>
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</table>

a All the reactions were performed in duplicate at r.t., using ethyl iodoacetate (2 equiv) and Me₂Zn (2 equiv). The catalyst was prepared by stirring ClMn(Salen) (R,R)-2 (20 mol%) and 4-phenylpyridine N-oxide (25 mol%) in t-BuOMe (0.04 M) for 1 h.
b Yield after chromatographic purification.
c The enantiomeric excess was evaluated by chiral HPLC analysis (AD and OD chiral column).

Scheme 3 Chloromanganese–Salen complex (R,R)-2 Reformatsky reaction with α-halo ketones.
action at room temperature for three hours, in the absence of 4-phenylpyridine N-oxide, gave an racemic product in 80% yield. The inclusion of the additive at room temperature or 0 °C did not improve the enantiomeric excess obtained and decreased the yield. Further studies on this class of highly functionalized ketones are in progress, and we hope to improve the enantiomeric excess, practicability, and selectivity with a extensive optimization of new tailored Mn(Salen) complexes.

\[ \text{4H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers, with residual CHCl, as the internal standard (\( \delta \) 7.27).} \]

\[ \text{13C NMR spectra were recorded on a Varian 50 MHz, Varian 75 MHz or Varian 100 MHz spectrometers with complete proton decoupling using CDCl, as the solvent and internal standard (\( \delta \) 77.0). MS spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification used 240–400 mesh silica gel. Analytical GC was performed on a Hewlett-Packard HP 6890 gas chromatograph, with a flame ionization detector and split-mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical HPLC was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190–600 nm), using a Daicel Chiralcel OD column (0.46 cm i.d. \( \times \) 25 cm) (Daicel Inc.) and a Daicel Chiralcel AD column (0.46 cm i.d. \( \times \) 25 cm) (Daicel Inc.). HPLC grade i-PrOH and hexane were used as the eluting solvents. LC were obtained with HPLC Agilent technologies HP1100 series, equipped with a diode array detector. Only a pre-column was used for purifying the products. All reactions were carried out under an N\(_2\) atmosphere in flame-dried glassware, using standard inert techniques to introduce reagents and solvents. All ketones were purified prior to use. All the other commercially obtained racemic or 0 °C did not improve the enantiomeric excess obtained and decreased the yield. Further studies on this class of highly functionalized ketones are in progress, and we hope to improve the enantiomeric excess, practicability, and selectivity with a extensive optimization of new tailored Mn(Salen) complexes.} \]

\[ \text{References} \]


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(9) Cozzi P. G., unpublished results.


(19) The combination of ClMn(Salen) with Me₂Zn, in the absence of iodoacetate and ketones, gives a rapid development of a yellow color, indicating the presence of Zn(Salen). In addition, by quenching the reaction with water, free Salen ligand is observed by TLC analysis. ClMn(Salen) is quite stable in the presence of water.


