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First enantioselective one-pot, three-component imino Reformatsky reaction*

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Abstract: The Reformatsky reaction is the well-recognized carbon–carbon bond-forming reaction of α-halo esters with aldehydes or ketones in the presence of Zn metal to give β-hydroxy esters. Recently, it has been reported that Rh- and Ni-catalyzed Reformatsky reaction, in which R_2Zn (R = Me, Et) acts as the Zn source, reacted smoothly with carbonyl compounds and imines. Taking advantage of *N*-methylephedrine as a cheap and recoverable chiral ligand, we have discovered the first homogeneous enantioselective Ni-catalyzed imino Reformatsky reaction. The process is a one-pot, three-component reaction, in which Me_2Zn plays multiple roles as dehydrating agent, reductant, and coordinating metal. Broad scope, high enantiomeric excess, and a simple procedure are adding value to our findings.

Keywords: Reformatsky; Me_2Zn; nickel; *N*-methylephedrine; amino esters.

The preproteomic/genomic epoch for drug discovery requires the interactive screening of drug candidates against biological targets followed by the sequential optimization of the lead compounds. Chiral compounds are nowadays tested owing to the possible different behavior of both enantiomers [1]. Therefore, chiral targets are the compounds focused in the development of new synthetic strategy. In order to maximize the synthetic efficiency, the use of new tools, such as parallel automatic synthesis, combinatorial chemistry, and high-throughput screening are essential. Although the diversity-oriented synthesis [2] has permitted the identification of new leads [3], often in the strategy to produce a compound or a library, only two reagents react in each synthetic step. A complementary strategy and simple solution to the drawbacks of the iterative strategy is the use of multicomponent reactions (MCRs) [4], which are more efficient, due to their superior atom economy, selectivity, as well as a minor level of by-products. The Mannich reaction, discovered in 1912, is one of the most important MCRs in organic synthesis [5], even if the entioselective multicomponent Mannich reaction was scarcely developed. The reaction between a chelating aniline derivatives, aldehydes, and silyl enolates is catalyzed by Zr complexes, as reported by Kobayashi [6] (Scheme 1) or by Ag complexes as described by Snapper and Hoveyda [7]. Both these remarkable examples involved the use of a silyl enolate prepared separately. A great advance in performing a Mannich-type reaction in multicomponent fashion will be the formation of the enolate at an invariably predetermined site, under neutral conditions. Recently, Honda and coworkers developed a 3CR version of their Rh Reformatsky-type reaction [8], which affords amino esters in 45–85 % yields. In this interesting method, a Reformatsky reagent is generated in situ from bromo esters and diethylzinc in the presence of the Wilkinson catalyst and then reacted with an

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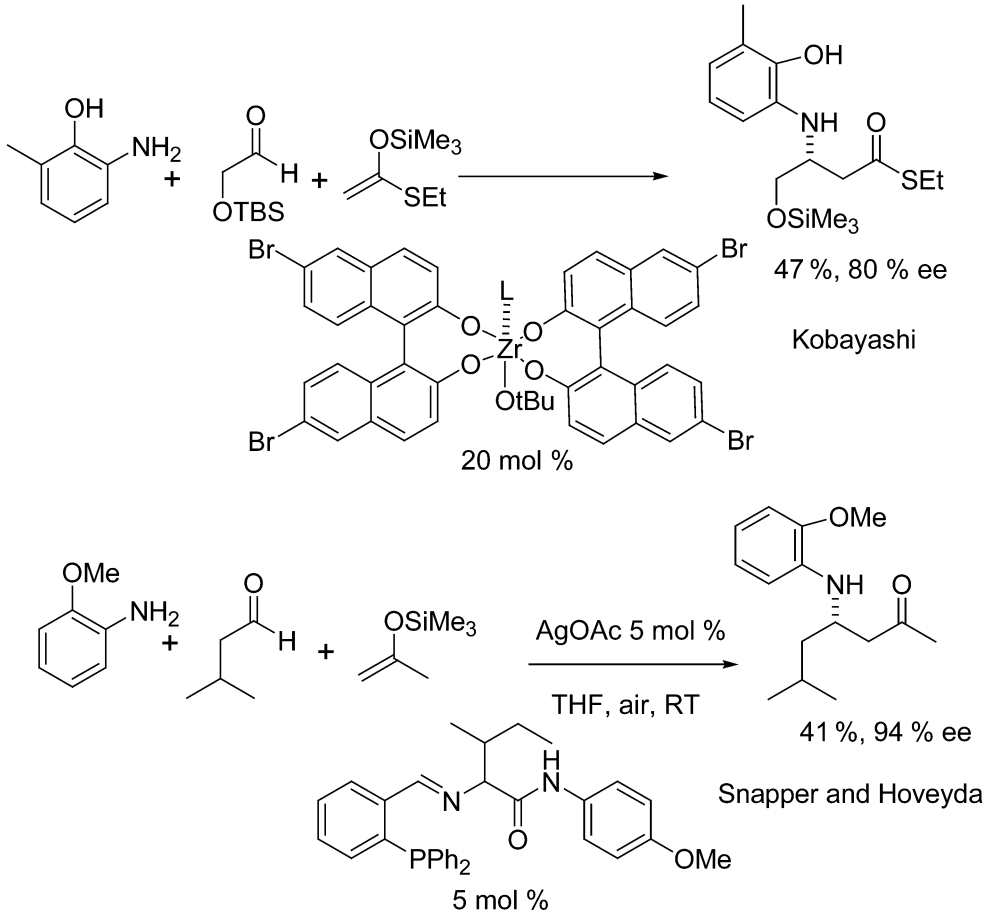
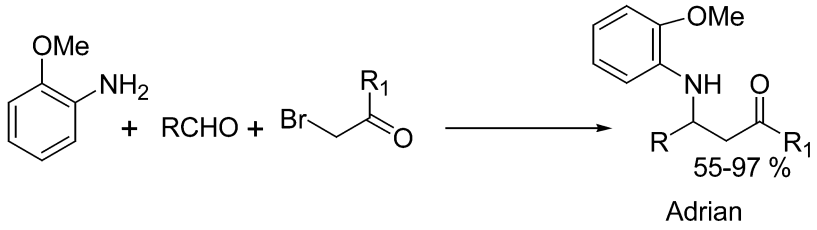
imine, also generated in situ. The reaction shows broad scope as enolizable and nonenolizable aldehydes were employed. The asymmetric extension of this reaction was also described by Honda [9] with the employing of the benzyl ether of (*R*)-phenylglicinol as chiral auxiliary. The reaction was highly diastereoselective, and only one diastereoisomer was isolated. However, after deprotection, the optically active β-amino acid was isolated in lower ee (59–85 %).



Scheme 1 Asymmetric multicomponent Mannich-type reaction.

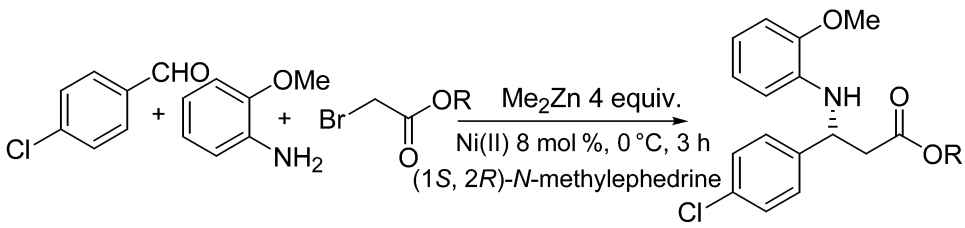
Adrian was able to develop an inexpensive 3CR Ni(II)-catalyzed Reformatsky reaction (Scheme 2) that works with all kinds of aldehydes, chelating *ortho*-methoxy aniline, and bromocarbonyl compounds [10]. The reaction was clean and afforded excellent yields.

The order of addition of the reagents in the one-pot reaction was crucial. The imine was prepared first, by in situ condensation of the aldehyde with the amine in the presence of an excess of Me_2Zn. The bromo carbonyl compound and the Ni(II) catalyst were then added to complete the reaction. It is remarkable that no by-products derived by the attack of Me_2Zn to the formed imines were isolated.



Scheme 2 The 3CR multicomponent Reformatsky reaction developed by Adrian.

We ask the question if chiral ligands would be compatible with the Adrian protocol, and we perform a model reaction, using *o*-methoxyaniline, *p*-chlorobenzaldehyde, ethyl bromo acetate in the presence of 4 equiv of Me_2Zn and 1 equiv of a chiral ligand. BINOL, BOX SALEN, and other privileged ligands tested gave disappointing results, while *N*-methylephedrine gave a good yield and 68 % ee. For this reason, we explored the Me_2Zn-mediated one-pot, three-component imino Reformatsky reaction using *N*-methylephedrine as the chiral ligand (Scheme 3). It is worth noting the multiple role played by Me_2Zn in the reaction: (a) Me_2Zn is the dehydrating agent responsible for the formation of the imine in situ, (b) Me_2Zn is able to reduce the Ni(II) salt to Ni(0), (c) Me_2Zn reacts with the incipient nickel enolate to form the reactive zinc enolate and, finally, (d) Me_2Zn is able to coordinate *N*-methylephedrine, the amino alcohol used as the chiral ligand. Thus, Me_2Zn in the amounts of 4 equiv, on the basis of its multiple role, and in order to ensure good enantiomeric excess (ee), 1.5–1.6 equiv of *N*-methylephedrine were employed in our process. *N*-methylephedrine can easily be separated from the adduct by acidic work-up, and recovered followed by extraction of the aqueous alkaline layer. We tested several solvents for our processes; in general, coordinating solvents such as THF completely inhibit the reaction, while CH_2Cl_2 and toluene give better results. The $RhCl(PPh_3)_3$ complex introduced by Honda in his homogeneous Reformatsky-type reaction also promotes the addition, although the product was isolated in decreased ee's compared to those obtained in the presence of Ni complexes. Different bromo esters could be employed, and similar ee's were obtained with all types of ester examined. Toluene was selected as the reaction solvent in function of the slightly better results obtained, and the scope of the reaction was investigated. The reaction shows broad scope, since aromatic, aliphatic, unsaturated, and heterocyclic aldehydes are reactive, giving good to excellent ee (up to 92 %, Fig. 1). Although the yields were generally moderate, only unreacted aldehydes and *o*-methoxy aniline were isolated. We have established the (*R*) absolute configuration of the products obtained using (1*S*,2*R*)-*N*-methylephedrine as the chiral ligand in the case of aliphatic and aromatic aldehydes (isopropyl and phenyl), optimizing the general procedure of deprotection of 2-methoxyamines, developed by Snapper and Hoveyda, which uses $PhI(OAc)_2$ [11]. In general, CAN or other oxidative cleavages of *o*-methoxy aniline afforded lower yields.



Scheme 3 Asymmetric multicomponent imino Reformatsky reaction.

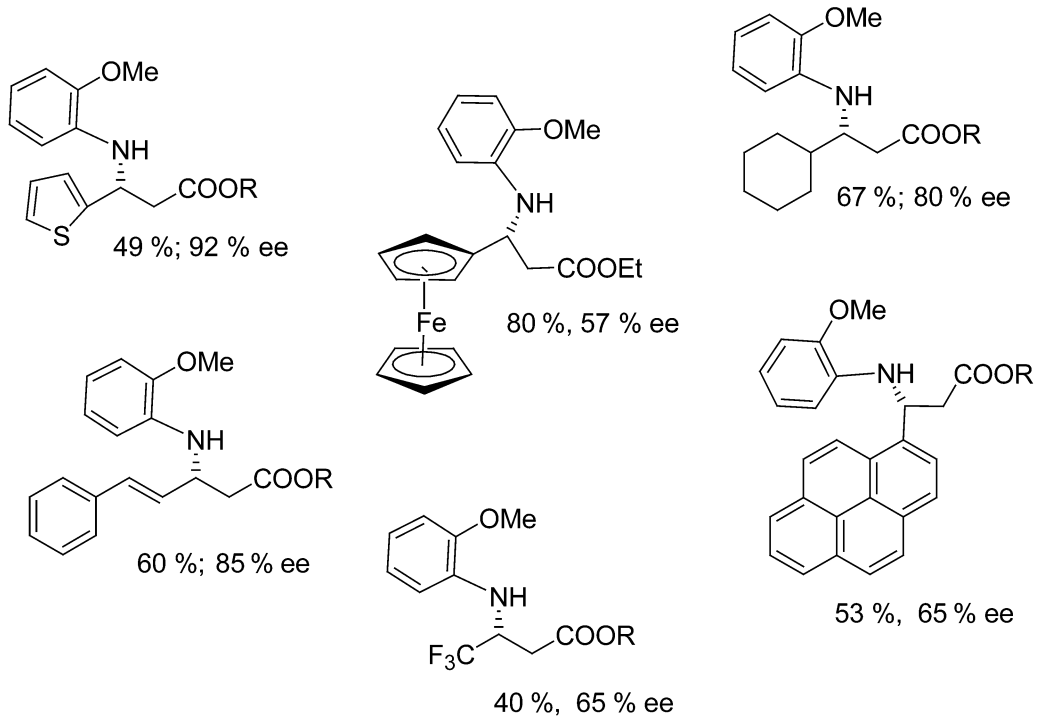


Fig. 1 Examples of various enantioenriched β-amino esters prepared with the enantioselective imino Reformatsky reaction.

Other amino alcohols have been tested, but lower ee's were observed in the model reaction [12].

It is worth noting that the high flexibility of our method allows the preparation of unconventional, optically active β-amino esters. For example, ferrocene could be readily inserted for preparing redox active β-amino esters [12]. However, in the case of the electron-rich imines obtained by the reaction with pyrene aldehyde and ferrocene aldehyde, a stepwise synthesis is necessary [12]. Moreover, trifluoro-substituted β-amino esters are readily accessible by using 6–7 equiv of Me_2Zn and the commercially available trifluoroacetaldeyde hydrate, performing the reaction without isolation of the gaseous trifluoroacetaldeyde [12].

In conclusion, we have developed the first practical and highly efficient, enantioselective one-pot, three-component imino Reformatsky reaction, giving β-amino esters in moderate to good yields. The reaction requires inexpensive Ni salts, bromo esters, and *N*-methylephedrine as the chiral ligand, which could be completely recovered after the work-up of the reaction, ready to be recycled.

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