Catalytic Enantioselective Aza-Reformatsky Reaction with Cyclic Imines

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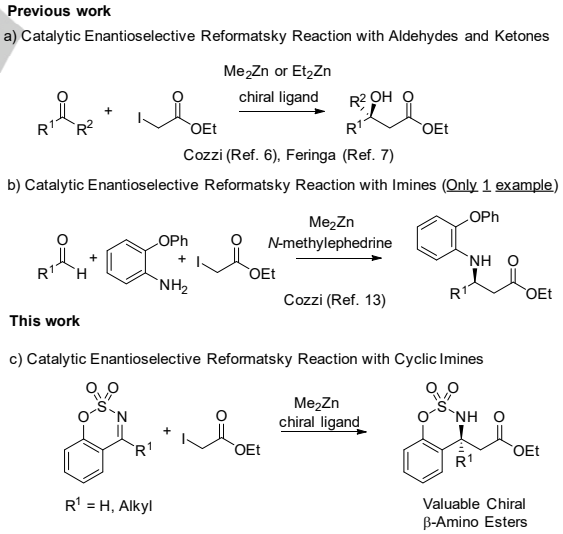
Abstract: A catalytic highly enantioselective aza-Reformatsky reaction with cyclic aldimines and ketimines for the synthesis of chiral β-amino esters with good yields and excellent enantioselectivities is reported. A readily available diaryl prolinol is used as a chiral ligand, $ZnMe_2$ as a zinc source and ethyl iodoacetate as reagent in the presence of air atmosphere. The reaction with cyclic ketimines generates a quaternary stereocenter with excellent levels of enantioselectivity. Furthermore, five-membered *N*-sulfonyl ketimines were used as electrophiles with good enantiomeric excesses, under the optimized reaction conditions. Moreover, several chemical transformations were performed with the chiral β-amino esters.

The classical Reformatsky reaction, discovered in 1887, provides a convenient synthesis of β-hydroxy esters through a zinc mediated reaction between α-haloacetates and aldehydes or ketones.[1,2] Since its introduction, more than 130 years ago, this reaction is a powerful methodology for C-C bond formation with a wide application in organic synthesis, due to the remarkable functional group tolerance and mild reaction conditions. In recent years, Reformatsky reaction has achieved renewed interest from the development of a homogeneous Reformatsky reaction based in the use of Me_2Zn or Et_2Zn introduced by Honda and coworkers in 2000.[3] In this context, asymmetric homogeneous Reformatsky reactions are known, but generally stoichiometric amounts of chiral ligands are used.[4] Recently, advances in the development of catalytic enantioselective methodologies for Reformatsky reactions,[5] for the synthesis of chiral β-hydroxy esters, were introduced by the groups of Cozzi[6] and Feringa[7] (Scheme 1a). Imines can be used as electrophiles for the Reformatsky reaction instead of aldehydes or ketones, as Gilman and Speeter disclosed 70 year ago.[8,9] However, this transformation is problematic, because often affords a mixture of β-amino esters and β-lactams. Consequently, the catalytic enantioselective aza-Reformatsky reaction is scarcely explored, despite its potential for the synthesis of chiral β-amino acids.[10] Chiral β-amino acids are an extremely important class of compounds in organic and medicinal chemistry. They are key structural elements of peptides or peptidomimetics.[11] Furthermore, β-amino acids are intermediates or precursors of biologically active compounds such as β-lactams, the most important class of antibiotics.[12]
Only one example of catalytic enantioselective aza-Reformatsky reaction is described in the literature. Cozzi, in 2006,[13] described the first catalytic enantioselective one-pot three-component aza-Reformatsky using *N*-methylephedrine (20-30 mol %) as chiral ligand obtaining highly enantioenriched β-amino esters (Scheme 1b).[14] However, in order to have high ee, *o*-phenoxyaniline was used, and the version with ketimines was unexplored in this report. In the context of aza-Reformatsky reaction, the addition of α-haloacetates to cyclic imines is unkown, despite its potential for the synthesis of optically pure *N*-heterocycles. Furthermore any ketimine has been used in such reactions. The use of this kind of electrophiles represents a synthetic challenge owing to their low reactivity, steric bulkiness and the associated difficulty with stereochemical control. Sulfamidates represent an interesting class of amine derivatives present in some pharmaceuticals and biological active compounds[15] and also play an important role as building blocks for organic synthesis.[16] We envisioned the use of cyclic imines such as benzoxathiazine 2,2-dioxides as electrophiles in the aza-Reformatsky reaction (Scheme 1c), because these compounds have a rigid structure that reduces the conformational mobility and avoid the E/Z isomerization, facilitating the stereodifferentiation and making them optimum partners for asymmetric catalysis. Recently, these cyclic imines have proven to be versatile building blocks in asymmetric synthesis and different enantioselective addition of nucleophiles have been described for the synthesis of chiral benzo-fused cyclic sulfamidate heterocycles.[17]



Scheme 1. Catalytic enantioselective Reformatsky reactions.

Herein, we disclose our results on the enantioselective addition of ethyl iodoacetate mediated by Me_2Zn to cyclic imines (aldimines and ketimines). This represents the first catalytic enantioselective aza-Reformatsky reaction with ketimines. Notably, this protocol is operated under mild reaction conditions and delivers the chiral functionalized cyclic sulfamidates in high yields and high to excellent enantiomeric excesses.

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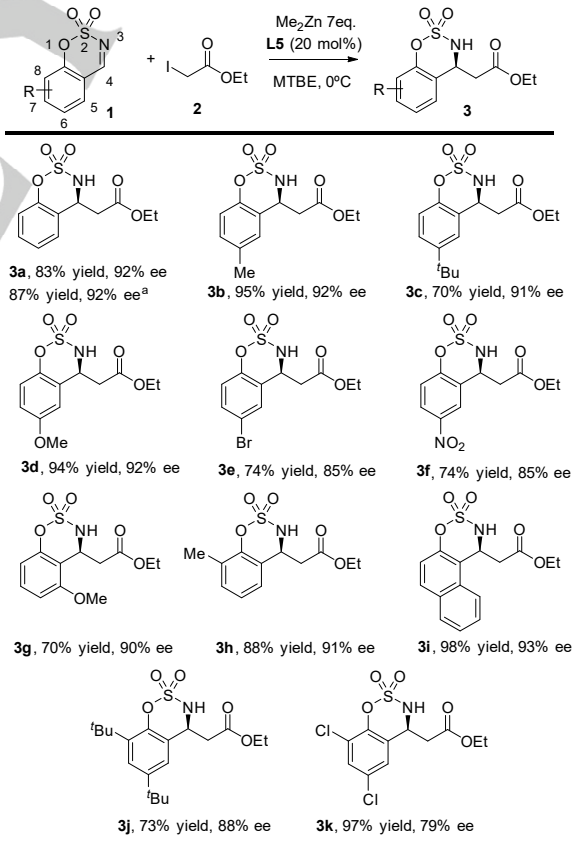
We started our studies with the reaction of ethyl iodoacetate (**2**)[18] with cyclic benzo[*e*][1,2,3]-oxathiazine 2,2-dioxide (**1a**) in the presence of chiral amino alcohols and mediated by Me_2Zn (Table 1). When quinine (**L1**) was used as a chiral ligand (entry 1, Table 1), full conversion was achieved obtaining the corresponding β-amino ester **3a** with 84% yield, but as a racemic mixture. After, we tested *N*-methyl ephedrine **L2**, used by Cozzi,[14] and the corresponding product **3a** was obtained with good yield but poor enantiomeric excess (entry 2, Table 1).

Table 1. Optimization of the reaction conditions.

Entry[a]	**L** (X mol%)	Solvent	T (ºC)	Yield (%)[b]	Ee (%)[c]
1	**L1** (20 mol%)	Et_2O	rt	84	0
2	**L2** (20 mol%)	Et_2O	rt	79	10[d]
3	**L3** (20 mol%)	Et_2O	rt	74	75
4[e]	**L3** (20 mol%)	Et_2O	rt	70	73
5[f]	**L3** (20 mol%)	Et_2O	rt	88	60
6	**L3** (20 mol%)	MTBE	rt	91	75
7	**L3** (20 mol%)	*i*Pr_2O	rt	87	69
8	**L3** (20 mol%)	THF	rt	42	28
9	**L3** (20 mol%)	Toluene	rt	95	70
10	**L3** (20 mol%)	CH_2Cl_2	rt	95	55
11	**L3** (20 mol%)	MTBE	0	74	80
12	**L3** (20 mol%)	MTBE	-10	96	77
13	**L4** (20 mol%)	MTBE	0	88	79
14	**L5** (20 mol%)	MTBE	0	86	92
15	**L6** (20 mol%)	MTBE	0	96	80
16	**L5** (10 mol%)	MTBE	0	89	87

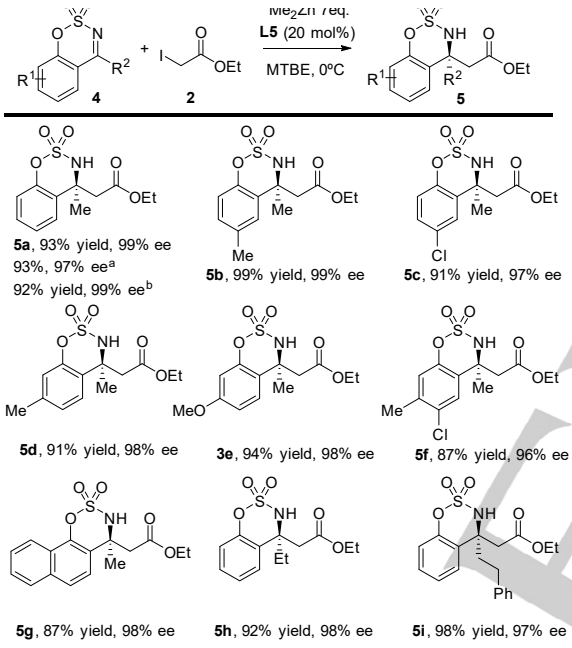
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.20 mmol), Me_2Zn (7 eq.) and ligand (x mol%) in 1 mL of solvent under air atmosphere. [b] Isolated yield after column chromatography. [c] Determined by HPLC using chiral stationary phase. [d] Opposite enantiomer was obtained. [e] 3 equivalents of Me_2Zn were used. [f] 7 equivalents of Et_2Zn were used.

In view of the poor results with chiral aminoalcohols bearing a tertiary amine, we focused our attention in the readily available (*S*)-diphenylprolinol (**L3**)[19] bearing a secondary amine. To our delight, when 20 mol% of ligand **L3** was used, product **3a** was gained with good yield (74%) and with a promising level of enantioselectivity (75% ee, entry 3). We try to decrease the amount of Me_2Zn to 3 equivalents, but unfortunately the yield and the enantiomeric excess were lower (entry 4). Furthermore, Et_2Zn was used as the zinc source in the model reaction (entry 5), obtaining better yield (88%) but with considerably lower enantioselectivity (60% ee). Consequently, we followed the optimization of the reaction conditions using 7 eq. of Me_2Zn. A solvent screening (entries 6-10) showed that ethereal solvents performed the reaction with the best enantioselectivities. Et_2O and MTBE, afforded the product **3a** with the same ee (75% ee), but the best yield (91%) was obtained when MTBE was used as a solvent. Therefore, MTBE was chosen as a solvent for a temperature screening (entries 11-12), observing the best enantioselectivity at 0 ºC (80% ee). At this point, our efforts to optimize the reaction conditions were aimed at exploring other commercially available diarylprolinol ligands (**L4-L6**, entries13-15) in order to improve the enantiomeric excess. Gratifyingly, (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol **L5** exhibited the best enantioselectivity affording product **3a** in 86% yield and 92% ee. A reduction of the catalyst load to 10 mol% had a slightly deleterious effect on the enantioselectivity of the reaction (87% ee, entry 16).



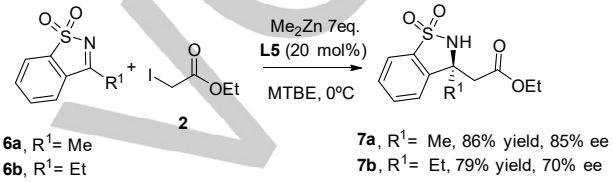
Scheme 2. Scope of the aza-Reformatsky reaction with cyclic aldimines: **1** (0.1 mmol), **2** (0.2 mmol), Me_2Zn (7 eq.) and **L5** (20 mol%) in 3 mL of MTBE. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase. [a] 0.4 mmol reaction scale.

With the optimized conditions in hand, the aza-Reformatsky reactions of a variety of aldimines **1** with ethyl iodoacetate were carried out (Scheme 2). Various substituents in the 6-position in the phenyl ring of the cyclic imines **1**, such as methyl, *tert*-butyl, methoxy, bromo or nitro, were well tolerated under the reaction conditions, and the corresponding chiral β-amino esters **3** were obtained with good yields (70-95%) and high enantioselectivities (85-92%). Moreover, substituents in other positions such as 5 and 8, and even naphthyl rings, were well tolerated giving the reaction product with great enantiomeric excesses (90-93% ee). Furthermore, cyclic imines (**1j-1k**) with two substituents that provide steric hindrance, were suitable substrates for the aza-Reformatsky reaction, affording good enantiomeric excess (88% and 79% ee).



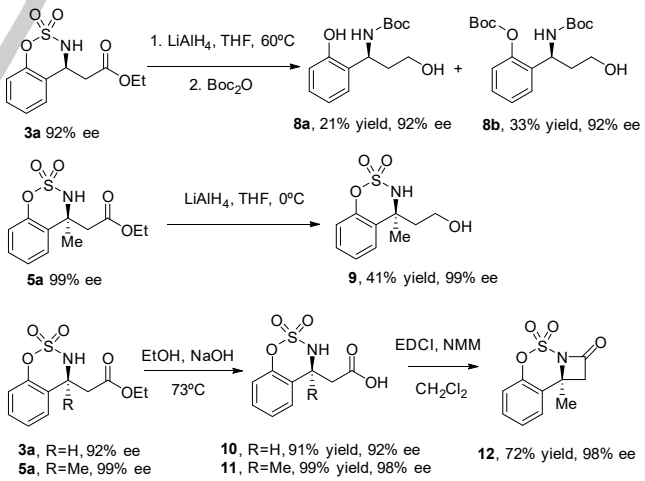
Scheme 3. Scope of the aza-Reformatsky reaction with cyclic ketimines: **4** (0.1 mmol), **2** (0.2 mmol), Me_2Zn (7 eq.) and **L5** (20 mol%) in 3 mL of MTBE. Isolated yields after column chromatography. Enantiomeric excesses were determined by HPLC using chiral stationary phase. [a] 10 mol% of **L5** was used. [b] 0.4 mmol reaction scale.

Once we have studied the aza-Reformatsky reaction with a variety of aldimines **1**, we decided to study the more challenging ketimines **4** (Scheme 3). To the best of our knowledge, ketimines have been never used in catalytic enantioselective aza-Reformatsky reaction probably due to their low reactivity and low control of stereoselectivity. However, we decided to test under the reaction conditions the corresponding 4-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide **4a** derived from *ortho*-hydroxyacetophenone. To our delight, compound **4a** reacted smoothly and the corresponding β-amino ester **5a**, bearing a quaternary stereocenter was gained with high yield (93%) and excellent enantioselectivity (99% ee). When the catalyst loading was reduced to 10 mol%, the enantioselectivity was still excellent (97% ee). Encouraged by the results for the Reformatsky reaction with ketimine **4a**, we decided to expand the methodology to other cyclic ketimines. A range of substituted ketimines efficiently participated in the reaction using the optimized conditions with excellent results in terms of reactivity and enantioselectivity. Introduction of substituents in the aromatic ring of the ketimines revealed that both electron-donating and withdrawing groups were well tolerated at various positions on the ring (**5b-5f,** 96-99% ee). A naphthyl substrate (**4g**) also gave the corresponding product **5g** with 87% yield and 98 % of enantiomeric excess. Furthermore, we explored other alkyl substituents (Et or $PhCH_2CH_2$-) in 4-position of ketimines **4**, giving the corresponding β-amino esters **5h** and **5i** with 98 and 97% ee, respectively.



Scheme 4. Enantioselective aza-Reformatsky reaction with cyclic *N*-sulfonyl ketimines **6**.

Having stablished the highly enantioselective aza-Reformatsky reaction of six-membered cyclic ketimines, we turned our attention to five-membered cyclic *N*-sulfonyl ketimines for the synthesis of chiral benzosultams. The enantioselective aza-Reformatsky reaction with cyclic ketimines **6** underwent smoothly, and the corresponding chiral β-amino ester **7** were obtained with good yields and enantioselectivities (Scheme 4).

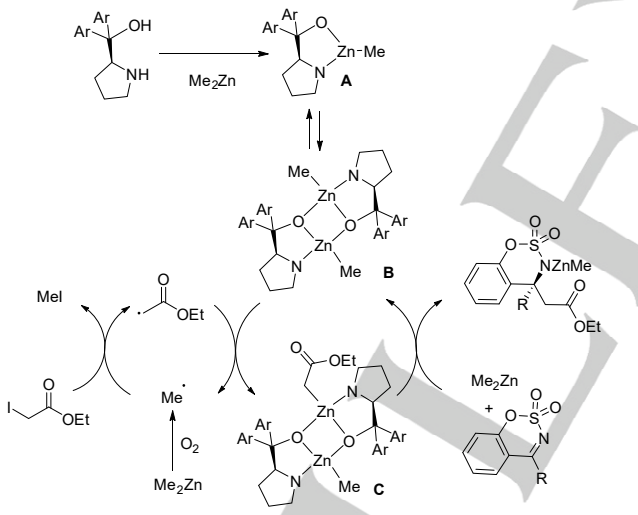


Scheme 5. Synthetic transformations. Boc= *tert*-Butyloxycarbonyl; THF= Tetrahydrofuran; EDCI= 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; NMM= *N*-Methylmorpholine.

To highlight the synthetic utility, we have applied several chemical transformations for the synthesis of interesting chiral compounds (Scheme 5). For example, the reduction of the ester

moiety and ring opening of the benzosulfamidate **3a**, give the aminoalcohols **8a** and **8b**, with moderate yield but preserving the enantiomeric excess. Chiral amino alcohol **9**, was synthesized by reduction of the β-amino ester at low temperature. The β-amino acids **10** and **11** were prepared by simple saponification with good yields and without loss of optical purity. Furthermore, the chiral β-lactam **12** with three fused cycles and a quaternary stereocenter was prepared from the β-amino acid **11**, in 72% yield and 98% ee.

In order to explain our results, we proposed the catalytic cycle depicted in Scheme 6. This catalytic system is based on the catalytic cycle proposed by Cozzi[6,13] and Feringa[7] for enantioselective Reformatsky reactions and the zinc intermediates proposed by Noyori.[20] Ligand **L5** is deprotonated by Me_2Zn to generate the complex **A**, which is in equilibrium with the dimer **B**. The addition of ethyl iodoacetate is accelerated in the presence of Me_2Zn and oxygen, through a cycle where Me_2Zn is acting as a source of methyl radicals which react with ethyl iodoacetate giving ethyl acetate radicals.[21-23] Complex **C** is generated after the addition of the ethyl acetate radical to dimer **B**. We believe that the active catalytic species is the complex **C** due to the moderate positive non-linear effect observed when correlating the enantiopurity of the aza-Reformatsky product **3a** with the enantiopurity of ligand **L5**.[24] Complex **C** assisted the nucleophilic addition of the ethyl iodoacetate to the *Si* face[25,26] of the cyclic imine affording the β-amino ester and regenerating the dimer **B**.



Scheme 6. Proposed catalytic cycle for the aza-Reformatsky reaction.

We have developed the first highly enantioselective catalytic aza-Reformatsky reaction with cyclic imines. In our methodology, cyclic aldimines and ketimines can be used as electrophiles obtaining chiral β-amino esters with excellent enantiomeric excesses. Our approach represents the first catalytic enantioselective aza-Reformatsky reaction with ketimines, leading to β-amino esters bearing a quaternary stereocenter. Moreover several transformations have been done with the corresponding chiral β-amino esters obtained.

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Keywords: asymmetric catalysis • Reformatsky reaction • zinc • cyclic ketimines • β-amino ester

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