Enantioselective Aza-Reformatsky Reaction with Ketimines.

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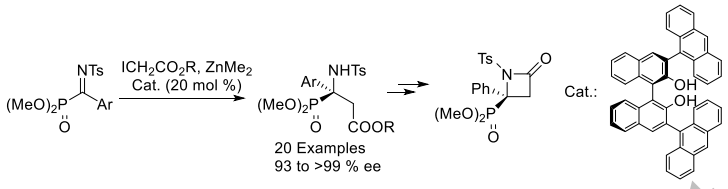


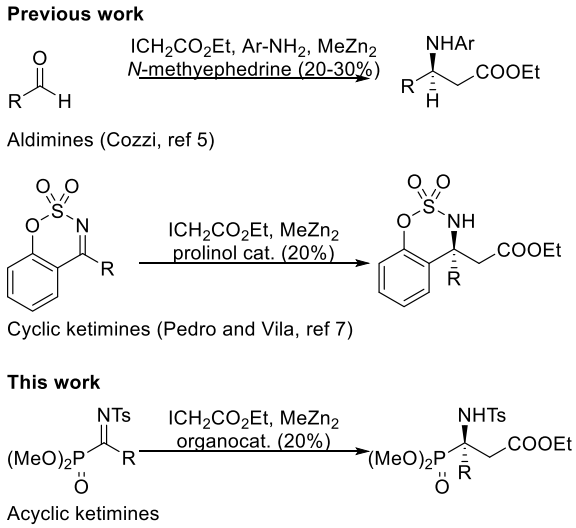
ABSTRACT: Here, an enantioselective aza-Reformatsky reaction using acyclic ketimine substrates is presented. Using α-phosphorated ketimines as electrophile substrates and a simple BINOL derived ligand, phosphorated analogs of aspartic acid holding chiral tetrasubstituted carbons are efficiently obtained with excellent enantioselectivity through an asymmetric organocatalytic Reformatsky-type reaction. The phosphorated analogs of aspartic acid have been used for the synthesis of phosphorus-containing enantiopure tetrasubstituted β-lactams.

Reformatsky reaction is a valuable synthetic process that is widely used for the effective formation of C-C bonds.[1] This transformation consists in a nucleophilic addition, in general to aldehyde or ketone substrates, of a zinc enolate, which is generated *in situ* through a metal insertion into activated carbon halides.[2] The discovery that organozinc species can be used as the metal source,[3] offered more convenient homogenous conditions for this reaction and, since then, many efforts have been made in developing catalytic systems for the enantioselective Reformatsky reaction using ketones and aldehydes.[4] Imines are, however suitable substrates for this reaction, providing access to β-amino acid derivatives in a simple synthetic protocol. The first catalytic enantioselective imino-Reformatsky reaction was reported by Cozzi in 2006 using *in situ* preformed aldimines and 20-30% of *N*-methylephedrine as chiral ligand (Scheme 1).[5]

Although not strictly catalytic, more recently Ando *et al.* have reported the synthesis of α,α-difluoro-β-lactams by an imino-Reformatsky protocol promoted by a 75% of aminoalcohol ligands.[6] Latterly, Pedro and Vila *et al.* have performed successful imino-Reformatsky processes with cyclic imines using a 20% of prolinol derived ligand.[7] Remarkably, their catalytic system is equally effective when cyclic ketimines are used as substrates, which allows the synthesis of quaternary cyclic β-aminoesters with excellent ees (Scheme 1).

Due to the poor electrophilic character of ketimine carbons and the additional steric hindrance on the substrate, the formation of tetrasubstituted carbons from ketimines is always a challenging task. In addition, the enantiotopic faces of ketimines are not as easily discriminated as those of aldimines when asymmetric synthesis is sought.[8] These obstacles are vitally important when acyclic substrates are used. In this context, we reported recently the organocatalyzed nucleophilic addition of cyanide or nitromethane to phosphorated ketimines[9] and the diastereoselective addition of organometallic reagents to TADDOL derived α-iminophosphonates[10] for the asymmetric preparation of tetrasubstituted α-aminophosphonate derivatives.

Scheme 1. Precedents in enantioselective aza-Reformatsky reaction.



In this case, we were intrigued about the possibility of accessing to phosphorated analogs of aspartic acid holding tetrasubstituted carbons, using α-ketiminophosphonate as electrophile substrates in an asymmetric aza-Reformatsky reaction (Scheme 1). As far as we know there are not examples of such reaction using acyclic ketimines as substrates.

Moreover, it is well known that α-aminophosphonates are an important class of compounds that can behave as stable analogs of the transition state of peptide cleavage. Due to this fact, they

often inhibit enzymes implicated in proteolysis processes and, for this reason, α-aminophosphonic acids derivatives and their phosphapeptides show an assorted biological activity.[11] The biological activity of drugs in general[12] and α-aminophosphonic acids in particular[13] is known to be strongly dependent on its absolute configuration and, for this reason, the development of new methods for the preparation of enantioenriched α-aminophosphonate derivatives is an important task in organic and medicinal chemistry.

Based in the zinc intermediates proposed by Noyori[14] and inspired by the mechanisms for other enantioselective Reformatsky processes proposed by Cozzi[5] and Feringa,[15] initially we chose several diols and β-aminoalcohols as chiral inductors in the aza-Reformatsky reaction of α-ketiminophosphonates (Figure 1). Our required imine electrophile substrates can be easily obtained by a formal oxidation of the parent tertiary α-aminophosphonates as reported.[9]

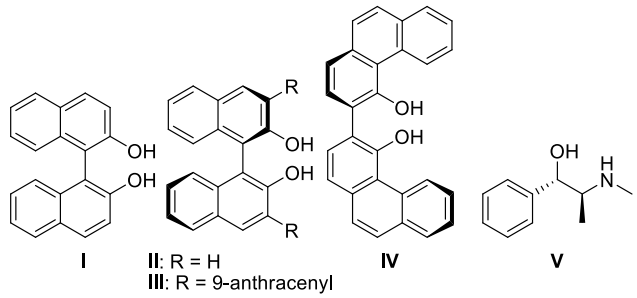


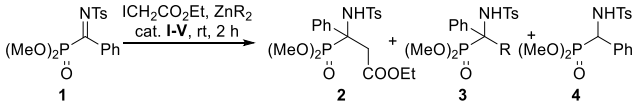
Figure 1. Ligands tested in this study.

For the optimization of the reaction conditions, first we studied the reaction of dimethyl α-iminophosphonate **1** with ethyl iodoacetate in the presence of an organozinc reagent and 20 mol % of racemic BINOL **I**. Depending on the organozinc reagent used in the reaction, besides the desired product **2**, compounds **3** and **4** were observed in the reaction mixture, resulting from a direct nucleophilic addition of organozinc reagent or the reduction of imine bond, respectively (Table 1).

First, when diethylzinc was used as the metal source in dichloromethane, the reaction proceeded fast but only reduced α-aminophosphonate **4** was observed (Table 1, Entry 1). Then, in order to minimize the ratio of β-hydride transfer that leads to the formation of the reduced product, dimethylzinc was used as metal source but only quaternary α-aminophosphonate **3** (R = Me) was observed, which presumably results from the nucleophilic addition of dimethylzinc to imine electrophile.

It is known that diakylzinc species under oxygen atmosphere are able to form the very reactive alkylperoxides (RZnOOR),[16] which are excellent radical initiators. In fact, some enantioselective Reformatsky reactions have been reported making use of organozinc reagents in the presence of air or oxygen.[5,15,17] Consequently, the reaction was performed in dichloromethane under dry air atmosphere using diethylzinc as the metal source but, although the reaction proceeded equally fast, again only reduced α-aminophosphonate **4** was observed (Table 1, Entry 3). Switching to dimethylzinc as the metal source, the formation of aza-Reformatsky product **2** was observed together with a 10% of 1,2-addition product **3** (Table 1, Entry 4). Due to the unfeasibility of β-hydride transfer reaction, no formation of reduced compound **4** was noticed in this case. Although the same ratio **2**:**3** was obtained when the reaction was performed in low polar or strong polar solvents such as toluene or *N*,*N*-dimethylformamide, respectively (Table 1, Entries 5-6), the amount of **2** could be increased using tetrahydrofurane or acetonitrile as solvents (Table 1, Entries 7-8).

Table 1. Optimization of the reaction conditions.



entry	solvent	R	cat.	Conversion/%	2:3:4[c]	ee/%[d]
1	CH_2Cl_2[a]	Et	**I**	100	0:0:100	-
2	CH_2Cl_2[a]	Me	**I**	100	0:100:0	-
3	CH_2Cl_2[b]	Et	**I**	100	0:0:100	-
4	CH_2Cl_2[b]	Me	**I**	100	90:10:0	-
5	toluene[b]	Me	**I**	100	90:10:0	-
6	DMF[b]	Me	**I**	100	90:10:0	-
7	THF[b]	Me	**I**	100	95:5:0	-
8	CH_3CN[b]	Me	**I**	100	97:3:0	-
9	CH_3CN[b]	Me	**II**	100	97:3:0	64
10	CH_3CN[b]	Me	**III**	100	97:3:0	99
11	CH_3CN[b]	Me	**IV**	100	97:3:0	38
12	CH_3CN[b]	Me	**V**	100	97:3:0	97

a) Under N_2 atmosphere. b) Under dry air atmosphere. c) Determined by ^{1}H-NMR. d) Determined by chiral HPLC.

Next, we tested enantiopure (*R*)-BINOL (**II**) as chiral ligand, under the optimal reaction conditions, but only modest enantioselectivity was obtained (Table 1, Entry 9). To our delight, when anthracenyl substituted BINOL ligand **III** was used in the same conditions, very high enantioselectivity was observed (Table 1, Entry 10). Surprisingly, the use of (*S*)-VAPOL (**IV**) resulted in decreased enantiomeric excess compared to simple (*R*)-BINOL (**II**) (Table 1, Entry 11). Finally, we even tested β-aminoalcohol derivative **V** that showed very good enantioselection (Table 1, Entry 12).

With the optimal reaction conditions in our hands, then we extended the scope of the enantioselective aza-Reformatsky reaction to differently substituted α-ketiminophosphonates **1** (Figure 2). Excellent enantiomeric excesses were obtained in all cases. The reaction tolerates the presence of *para* and *meta* alkyl substituents at the aromatic ring (Figure 2, **2b-c**) as well as strong electron donating groups at the *para* position of the aromatic imine (Figure 1, **2d**). Several halogen substituted aromatic ketimines were also successfully used in the reaction, including *para* substituted aromatic rings containing fluorine, chlorine or bromine (Figure 2, **2e-g**), *meta* substituted aromatic rings holding fluorine and chlorine (Figure 2, **2h-i**) as well as *ortho*-fluorophenyl substituted ketimines (Figure 2, **2j**).

Moreover, dichloro- and difluoro-phenyl substituted imines showed excellent enantioselectivities (Figure 2, **2k-m**) and even perfluorophenyl substituted substrates were tested with success using the same catalytic system (Figure 2, **2n**).

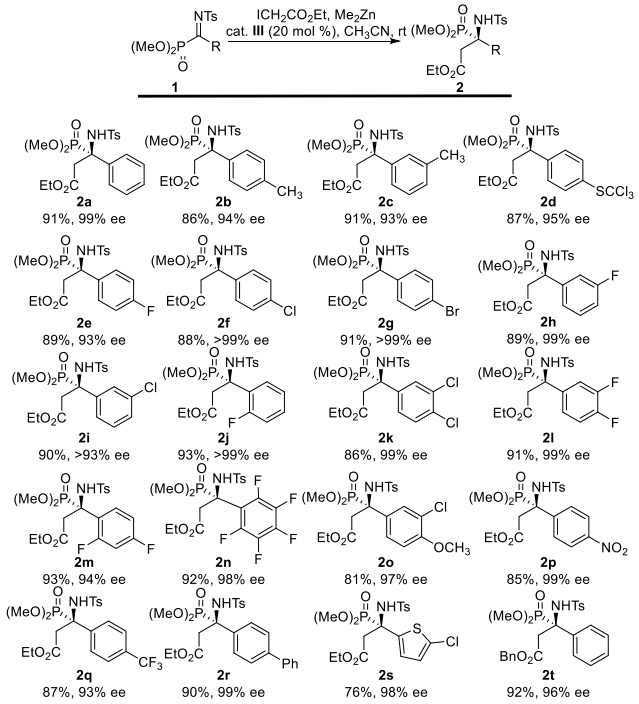


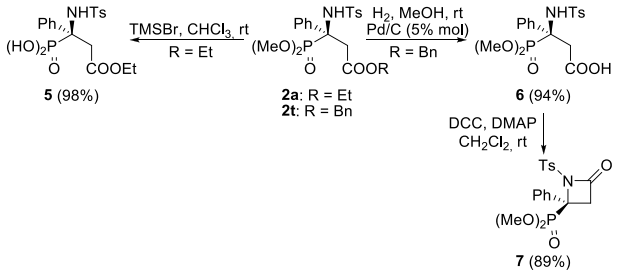
Figure 2. Scope of the reaction.

Furthermore, an excellent result was observed for imine **1o** holding an aromatic ring that is substituted with a chlorine and a strong electron donating methoxy group. Besides, good reactivity and excellent enantioselectivity is also obtained using aromatic imines substituted with electron withdrawing groups such as *p*-nitro or *p*-trifluoromethyl substituents (Figure 2, **2p-q**). The reaction can be also extended to the use of imines holding biphenyl or heteroaromatic substituents (Figure 2, **2r-s**). Finally, in order to further deprotect selectively the ester group, benzyl iodoacetate was used as reagent in the aza-Reformatsky reaction with our α-iminophosphonate substrates, again with an excellent result (Figure 2, **2t**).

Next, with the propose of illustrating the applications of our enantioenriched substrates, some synthetic transformations of α-aminophosphonate derivatives **2** were accomplished. A selective deprotection of the phosphonate group can be easily performed in a few hours using dimethylphosphonate derivative **2a** in the presence of trimethylsilylbromide[18] to afford α-aminophosphonic acid derivative **5** in very good yield.

For the selective deprotection of the ester group, we chose benzylic ester **2t** as substrate. A vigorous stirring of compound **2t** under hydrogen atmosphere in the presence of a catalytic amount of palladium yielded the expected phosphorylated β-amino acid derivative **6** in excellent yield. Finally, activation of carboxylic group in **6** with *N*,*N*-dicyclohexylcarbodiimide (DCC) in the presence of dimethylaminopyridine (DMAP) led to the formation of phosphorated β-lactam derivative **7** bearing a tetrasubstituted stereocenter.

Scheme 2. Synthetic applications of the phosphorated analogs of aspartic acid 2.



In order to authenticate the synthetic potential of our asymmetric methodology, a multi-gram scale reaction was performed for the synthesis of α-aminophosphonate **2t**. Thus, 1.00 grams of ketimine **1a** reacted with benzyl iodoacetate in the presence of 20 mol % of BINOL ligand **III** to yield the aza-Reformatsky product **2t** in 84% yield and 87% ee. With the aim of determining the absolute configuration of the stereogenic carbon of the major enantiomer in our substrates, using enantioenriched compound **2t**, a substantial amount of the enantiopure β-lactam **7** was prepared. A crystal of the major enantiomer of **7** was isolated and submitted to X-Ray diffraction analysis, revealing an *S* absolute configuration of the quaternary stereocenter (Figure 3).

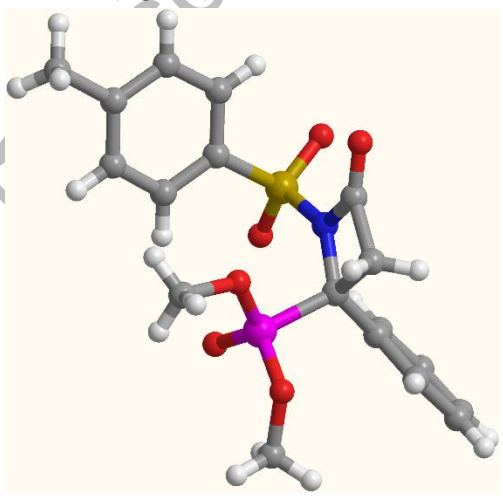


Figure 3. X-Ray structure of lactam 7 showing its absolute configuration (Grey: C, white: H, red: O, blue: N, purple: P)

In summary, although successful enantioselective Reformatsky reactions have been described during the last years using acyclic aldehydes, aldimines or ketones, we report here the first example of an enantioselective aza-Reformatsky reaction using acyclic ketimines as electrophile substrates. Phosphorated analogs of aspartic acid holding tetrasubstituted carbons, are efficiently obtained with excellent enantioselectivity, using α-ketiminophosphonates, with a simply functionalized BINOL ligand as the chiral inductor. In addition, besides that phosphorus-containing enantiopure tetrasubstituted β-lactams have not been reported so far, we describe here the first asymmetric synthesis of phosphorylated β-lactams using a catalytic approach.

ASSOCIATED CONTENT

Supporting Information

Cif file and thermal ellipsoid plot for **7** and full experimental details, characterization and copies of ^{1}H, ^{13}C, ^{31}P and NMR spectra for compounds **1**, **2**, **5**, **6** and **7** and ^{19}F NMR for compounds **1e,h,j,l,m,n,q** and **2e,h,j,l,m,n,q**.

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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