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Catalytic enantioselective aza-Reformatsky reaction with seven-membered cyclic imines dibenzo[*b*,*f*][1,4]oxazepines†

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A catalytic enantioselective aza-Reformatsky reaction is reported with cyclic dibenzo[*b*,*f*][1,4]oxazepines and ethyl iodoacetate leading to the synthesis of chiral ethyl 2-(10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepin-11-yl)acetate derivatives with excellent yields and high enantioselectivities (up to 98% yield and 97 : 3 er) using a readily available diaryl prolinol **L4** as the chiral ligand and Me_2Zn as the zinc source under an air atmosphere. Furthermore, different transformations were carried out with the corresponding chiral β-amino esters, preserving in all cases the optical purity.

Introduction

The dibenzo[*b*,*f*][1,4]oxazepine scaffold is an important pharmacophore and, over the last few years, has attracted much attention in the pharmaceutical industry and medicinal chemistry due to the fact that this structure is present in numerous compounds with a broad range of biological activities.[1] In this context, several 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives have been described possessing different physiological activities (Fig. 1). For example, Sintamil[2] and its analogue compound **A** have antidepressant activity, compound **B** is a progesterone receptor agonist,[3] while compound **C** presents antihistaminic activity.[4] Despite the importance of this pharmacophore, catalytic enantioselective methodologies to prepare optically pure 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives are scarce. So far, two organocatalyzed Mannich reactions,[5] an asymmetric alkynylation[6] and iridium catalyzed asymmetric hydrogenations of the corresponding seven-membered ketimines[7] have been reported. Consequently, the development of other catalytic enantioselective reactions to prepare these chiral seven-membered nitrogen heterocyclic compounds is an important aim in organic synthesis.

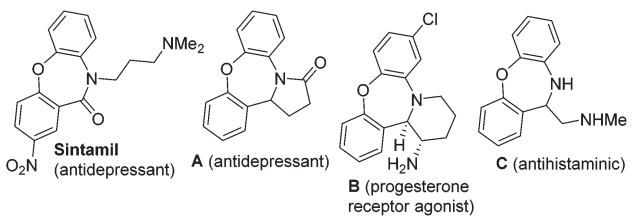

Fig. 1 Derivatives of cyclic amines containing the dibenzo[*b*,*f*][1,4]oxazepine motif.

On the other hand, chiral β-amino esters are a significant class of building blocks in synthetic chemistry, which have been used for the synthesis of optically pure β-amino alcohols or β-amino acids. Chiral β-amino acids[8] are key structural elements of peptides and peptidomimetics,[9] and are precursors of β-lactams.[10] The catalytic enantioselective Reformatsky[11,12] reaction using imines as electrophiles provides a suitable methodology for the synthesis of chiral β-amino esters. However, the catalytic asymmetric Reformatsky reaction with imines is hardly studied, in contrast to the corresponding reaction using aldehydes[13] or ketones.[14] Only two examples of the enantioselective aza-Reformatsky reaction have been described in the literature by Cozzi[15] and our group.[16] To the best of our knowledge, seven-membered cyclic imines have not been used as electrophiles in this reaction. We envisioned that the cyclic imines dibenzo[*b*,*f*][1,4]oxazepines would be interesting electrophiles for the barely studied asymmetric aza-Reformatsky reaction. Herein, we present our results using these seven-membered cyclic imines as substrates and ethyl iodoacetate as the reagent, in the presence of a readily available diaryl prolinol as the chiral ligand and Me_2Zn as the zinc source under an air atmosphere, providing chiral β-amino esters with high yields and enantioselectivities.

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Results and discussion

Our initial studies were focused on the addition of ethyl iodoacetate (**2**) to dibenzo[*b*,*f*][1,4]oxazepine **1a** in the presence of Me_2Zn and various chiral amino alcohols under an air atmosphere. As shown in Table 1, when 20 mol% of quinine (**L1**) was used in diethyl ether, 45% yield was obtained, providing the compound ethyl 2-(10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepin-11-yl)acetate **3a** with a poor enantiomeric ratio (43 : 57). Later, we tested *N*-methyl ephedrine **L2**, used by Cozzi,[15] and the corresponding β-amino ester **3a** was obtained with a moderate yield and higher enantiomeric ratio (34.5 : 65.5). However, this er was still unsatisfactory (entry 2, Table 1). Later, we decided to investigate the use of several commercially available chiral diaryl prolinols **L3–L6** (entries 3–6, Table 1). We observed higher enantioselectivities with this kind of ligand, obtaining the highest er (73 : 27) when (*S*)-bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol **L4** was used as the ligand. Therefore, we continued the optimization process with **L4**, testing different solvents (entries 7–15, Table 1). With ethereal solvents (iPr_2O, THF or MTBE) similar levels of enantioselectivities were obtained for compound **3a**.

Chlorinated solvents such as dichloromethane or dichloroethane lead to similar enantiomeric ratios, while chloroform gave lower yield and enantioselectivity. Finally, when EtOAc was used as the solvent, the corresponding chiral β-amino ester was obtained with good yield (63%) and the best enantioselectivity (79.5 : 20.5 er, entry 15). Therefore, EtOAc was chosen for further optimization. Lowering the reaction temperature to 0 °C improves the enantioselectivity (94 : 6 er), but the yield was low (22%). By increasing the number of the equivalents of ethyl iodoacetate, we could improve the yield (78%), keeping the enantioselectivity high (91 : 9 er) for the aza-Reformatsky reaction. However, when we lowered the temperature to −10 °C, the enantioselectivity increased but the yield was much lower (40%). Consequently, we decided to carry out the reaction at 0 °C. Furthermore, Et_2Zn was used as the zinc source in the model reaction (entry 19), obtaining good yield (75%) but a lower enantioselectivity (84 : 16 er). Working at lower concentrations (entry 21) had an improvement both in yield and enantioselectivity (97% yield and 93.5 : 6.5 er). A reduction of the catalyst load to 10 mol% had a slightly deleterious effect on the yield (92%) but not on the enantioselectivity of the reaction (93 : 7 er, entry 22).[17]

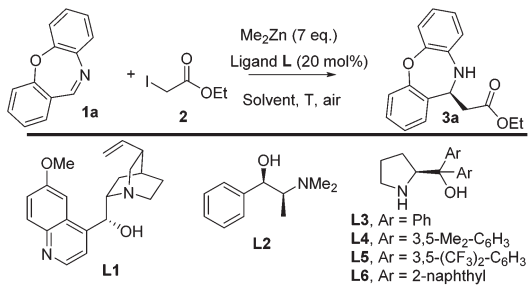
Under the optimized reaction conditions (entries 21 and 22, Table 1), a variety of substituted dibenzo[*b*,*f*][1,4]oxazepines were subjected to the aza-Reformatsky reaction (Scheme 1). A wide range of substituted cyclic imines **1**, with both electron-donating and electron-withdrawing substituents at different positions of the two aromatic rings, afforded the corresponding chiral β-amino esters **3a–3o** with high yields (up to 99%) and enantioselectivities (up to 97 : 3 er). For the cyclic imine **1k**, bearing two methoxy groups in the aromatic ring, a lower enantioselectivity was obtained (89.5 : 10.5 er) probably due to the presence of the methoxy group next to the C=N electrophilic bond. However, the yield was excellent (94% yield). Cyclic imines bearing a naphthyl ring (**1m–1o**) afforded the corresponding products with high enantiomeric ratios and excellent yields.[18]

The absolute configuration of the stereogenic center in compound **3o** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Fig. 2); the configuration of the rest of the products **3** was assigned on the assumption of a uniform mechanistic pathway.[19]

With the above successful results, we further investigated the aza-Reformatsky reaction of dibenzo[*b*,*f*][1,4]thiazepine **4** with ethyl iodoacetate (Scheme 2). Dihydrodibenzothiazine is also an important and widely used scaffold in medicinal chemistry,[20] although its synthesis using catalytic asymmetric procedures is limited to the asymmetric hydrogenation of the corresponding seven-membered ketimines.[21] When the cyclic imine **4** was used as a substrate, the corresponding β-amino ester **5** was obtained with excellent yield (95%) and high enantiomeric ratio (94.5 : 5.5).

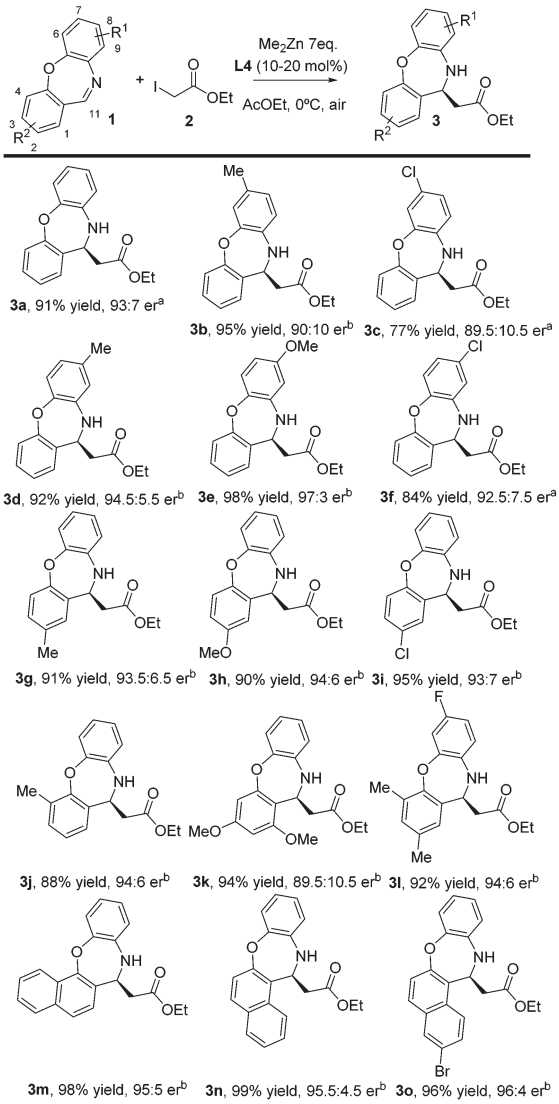
To highlight the synthetic utility of this methodology, we have applied several chemical transformations for the syn-

Table 1 Optimization of the reaction conditions[a]



Entry	Ligand (*x* mol%)	Solvent	*T* (°C)	Yield[b] (%)	er[c]
1	**L1** (20 mol%)	Et_2O	rt	45	43 : 57
2	**L2** (20 mol%)	Et_2O	rt	42	34.5 : 65.5
3	**L3** (20 mol%)	Et_2O	rt	57	67 : 33
4	**L4** (20 mol%)	Et_2O	rt	42	73 : 27
5	**L5** (20 mol%)	Et_2O	rt	71	69.5 : 30.5
6	**L6** (20 mol%)	Et_2O	rt	36	71.5 : 28.5
7	**L4** (20 mol%)	iPr_2O	rt	54	76.5 : 23.5
8	**L4** (20 mol%)	MTBE	rt	47	77.5 : 22.5
9	**L4** (20 mol%)	THF	rt	63	74.5 : 25.5
10	**L4** (20 mol%)	Toluene	rt	33	68.5 : 31.5
11	**L4** (20 mol%)	CH_2Cl_2	rt	44	76.5 : 23.5
12	**L4** (20 mol%)	$ClCH_2CH_2Cl$	rt	51	78 : 22
13	**L4** (20 mol%)	$CHCl_3$	rt	29	73 : 27
14	**L4** (20 mol%)	CH_3CN	rt	53	74 : 26
15	**L4** (20 mol%)	AcOEt	rt	63	79.5 : 20.5
16	**L4** (20 mol%)	AcOEt	0	22	94 : 6
17[d]	**L4** (20 mol%)	AcOEt	0	78	91 : 9
18[d]	**L4** (20 mol%)	AcOEt	−10	40	94 : 6
19[d,e]	**L4** (20 mol%)	AcOEt	0	75	84 : 16
20[d,f]	**L4** (20 mol%)	AcOEt	0	71	87 : 13
21[d,g]	**L4** (20 mol%)	AcOEt	0	97	93.5 : 6.5
22[d,g]	**L4** (10 mol%)	AcOEt	0	92	93 : 7

[a] **1a** (0.1 mmol), **2** (0.2 mmol), Me_2Zn (7 eq.) and ligand (*x* mol%) in 3 mL of solvent. [b] Isolated yield after column chromatography. [c] Determined by HPLC using the chiral stationary phase. [d] 3 equivalents of **2** were used. [e] 7 equivalents of Et_2Zn were used. [f] 1.5 mL of EtOAc was used. [g] 6 mL of EtOAc was used.



Scheme 1 Scope of the aza-Reformatsky reaction with dibenzo[*b*,*f*][1,4]oxazepines **1**: **1** (0.1 mmol), **2** (0.3 mmol), Me_2Zn (7 eq.) and **L4** (*x* mol%) in 6 mL of AcOEt. Isolated yields after column chromatography. Enantiomeric ratio was determined by HPLC using the chiral stationary phase. [a] 10 mol% of **L4** was used. [b] 20 mol% of **L4** was used.

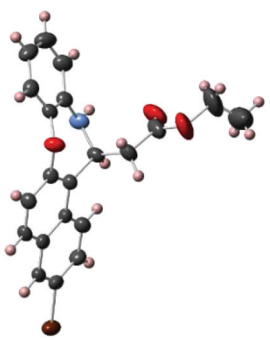
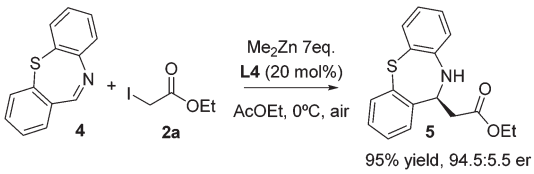
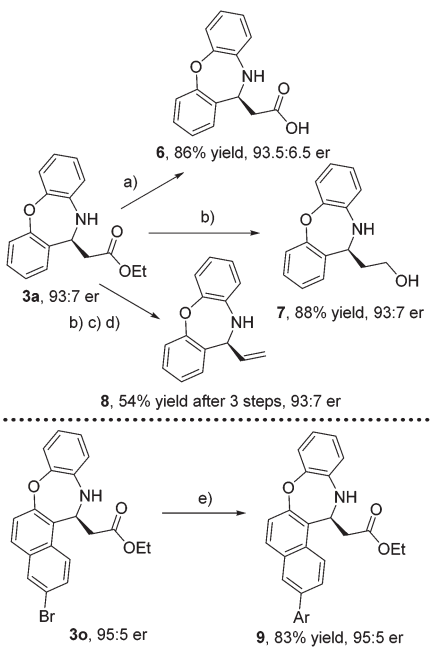


Fig. 2 X-ray structure of compound **3o**.



Scheme 2 Aza-Reformatsky reaction with dibenzo[*b*,*f*][1,4]thiazepine **4**: **4** (0.1 mmol), **2** (0.3 mmol), Me_2Zn (7 eq.) and **L4** (20 mol%) in 6 mL of AcOEt. Isolated yields after column chromatography. Enantiomeric ratio was determined by HPLC using the chiral stationary phase.

thesis of interesting chiral compounds bearing a dibenzo[*b*,*f*][1,4]oxazepine scaffold (Scheme 3). The ester moiety of product **3a** provides a convenient site for further modification. For example, chiral β-amino acid **6** was prepared in 86% yield and without the loss of optical purity by simple saponification of the ester moiety. Chiral amino alcohol **7** was synthesized by reduction of the β-amino ester with $LiAlH_4$. Furthermore, the interesting 11-vinyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine **8** was easily synthesized by a three step reaction sequence with an overall yield of 54% and maintaining the optical purity.[22] Finally, a Suzuki cross-coupling reaction was performed using (4-methoxyphenyl)boronic acid and the chiral 10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine **3o**, obtaining the corresponding chiral product **9** in 83% yield and 95 : 5 er.



Scheme 3 Synthetic transformations: (a) NaOH 1 M in EtOH at 75 °C. (b) $LiAlH_4$ in THF at 0 °C. (c) *o*-Nitrophenyl selenocyanate (2.4 eq.) and PBu_3 (2.5 eq.) in THF at rt. (d) 5 eq. of H_2O_2 (50% aqueous solution) in THF at 0 °C, and then at rt. (e) $ArB(OH)_2$ (2 eq.), K_3PO_4 (8 eq.) and $PdCl_2(PPh_3)_2$ (10 mol%) in DMF at 80 °C. Ar = *p*-$MeOC_6H_4$–.

Conclusions

In summary, we have developed a catalytic enantioselective aza-Reformatsky reaction with seven membered cyclic imines. In our methodology, dibenzo[*b*,*f*][1,4]oxazepines **1** and dibenzo[*b*,*f*][1,4]thiazepine **4** can be used as electrophiles obtaining chiral β-amino esters with high enantiomeric ratios. Our approach represents the first catalytic enantioselective aza-Reformatsky reaction with this class of cyclic imines. Moreover, several transformations have been made with the chiral β-amino esters obtained. Studies to further extend the scope of this reaction are currently underway in our laboratory.

Acknowledgements

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17 The reaction was tested in a 0.5 mmol scale (100 mg) using 10 mol% of the catalyst, obtaining the corresponding product **3a** in 95% yield and 93 : 7 er. However, when the reaction was scaled up to 2 mmol (400 mg) using 10 mol% catalyst, the corresponding product **3a** was obtained with 89% yield and 85 : 15 er.

18 The 11-methyldibenzo[*b*,*f*][1,4]oxazepine (a cyclic seven membered ketimine) was tested under the optimized reac-

tion conditions; however, poor conversion was observed (less than 10%) by ^{1}H NMR analysis of the crude reaction mixture.

19 CCDC 1530500 (for **3o**) contains the supplementary crystallographic data.

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