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Enantioselective Addition of Et_2Zn to Seven-Membered Cyclic Imines Catalyzed by a Zn(II)-(*R*)-VAPOL Complex

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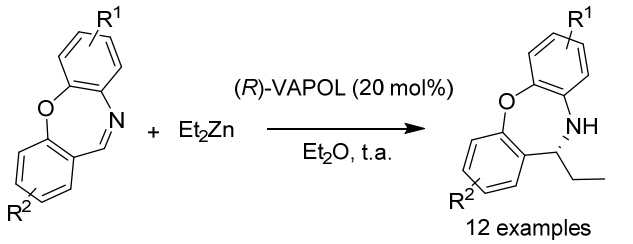

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Enantioselective Addition of Et_2Zn to Seven-Membered Cyclic Imines Catalyzed by a (*R*)-VAPOL-Zn(II) Complex.

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Zinc
Dibenzo[*b*,*f*][1,4]oxazepine
Asymmetric catalysis
VAPOL
Cyclic imine

ABSTRACT

Various substituted dibenzo[*b*,*f*][1,4]oxazepines underwent an enantioselective alkylation with Et_2Zn catalyzed by a (*R*)-VAPOL-Zn(II) complex. The corresponding chiral 11-ethyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives were obtained with good yields and moderate enantioselectivities. This represents the first example of enantioselective addition of Et_2Zn to cyclic aldimines.

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1. Introduction

Dibenzo[*b*,*f*][1,4]oxazepine derivatives are attractive compounds that recently have attracted huge attention from the pharmaceutical industry due to the wide spectrum of biological activities that present such compounds.[1] Among compounds containing the dibenzoxazepine scaffold are non-nucleoside HIV-1 reverse transcriptase inhibitors,[2] antidepressants,[3] analgesics,[4] anxiolytics[5] and a lachrymatory agent,[6] as well as a histamine H_4 receptor agonist,[7] PGE_2[8] and calcium[9] antagonists. In this context, 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives play an important role in medicinal chemistry and several derivatives have shown interesting biological activities (Figure 1), therefore their synthesis are of great interest in organic synthetic chemistry.[10] However, catalytic asymmetric methodologies for the synthesis of this kind of compounds are scarce in the literature. So far, only iridium-catalyzed asymmetric hydrogenation of the corresponding seven-membered cyclic ketimines,[11] as well as enantioselective Mannich,[12] aza-Reformatsky,[13] alkynylation[14] and propargylation[15] reactions of the seven membered cyclic aldimines have been described. Therefore, the development of new methodologies to synthesize optically pure 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives is highly desirable for synthetic organic chemistry.

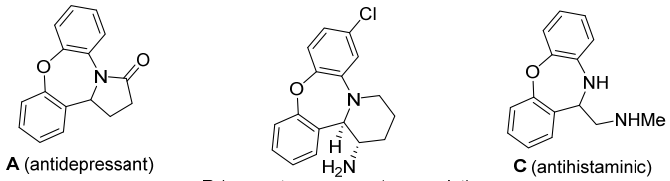

Figure 1. Examples of 11-substituted-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives with biological activities.

The catalytic asymmetric addition reactions of organometallic reagents to imines are a central processes in synthetic chemistry to prepare chiral amines,[16] which are important building blocks for pharmaceutical and medicinal chemistry.[17] In this context, the catalytic asymmetric addition of dialkylzinc reagents to imines is a convenient methodology to prepare chiral amines.[18] Several examples of the enantioselective addition of organozinc reagents to acyclic imines have been described in the literature.[19] However, the corresponding addition of dialkylzinc reagents to cyclic imines remains unexplored, to the best of our knowledge (Scheme 1). Hence, we present our results on the enantioselective addition of Et_2Zn to dibenzo[*b*,*f*][1,4]oxazepine derivatives, as a seven-membered cyclic imine, catalyzed by a (*R*)-VAPOL-Zn(II) complex in order to prepare chiral 11-ethyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives with good yields and moderate enantioselectivities.

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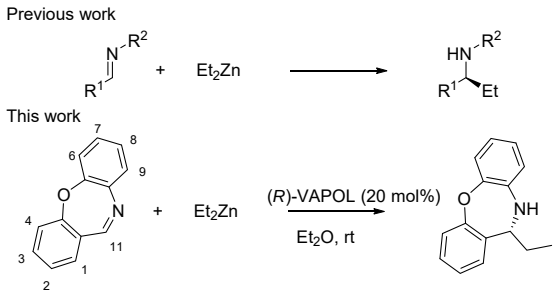


Scheme 1. Enantioselective addition of Et_2Zn to imines.

2. Results and discussion

Optimization studies were performed with the alkylation reaction of seven-membered cyclic imine **1a**, as the model substrate, with Et_2Zn in dichloromethane at room temperature. Several chiral Zn(II)-complexes, generated in situ from Et_2Zn and chiral ligands **L** (Figure 2), were tested and the results are summarized in Table 1.

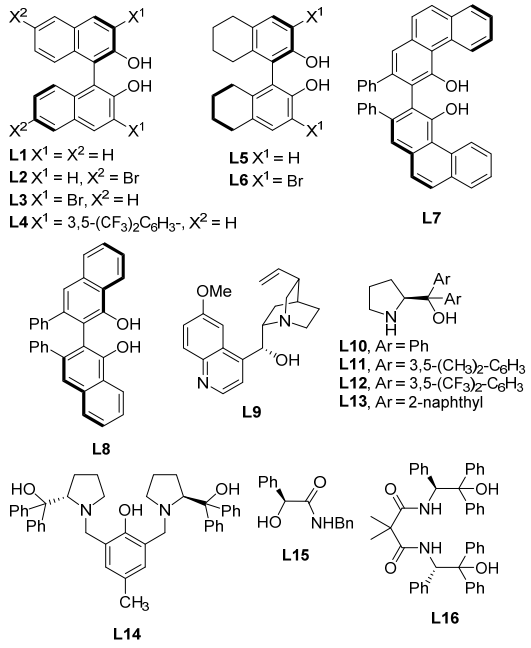
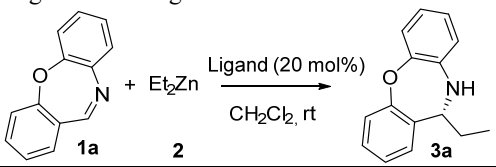


Figure 2. Chiral ligands evaluated.

First, a family of BINOL ligands (**L1**-**L6**, entries 1-6 Table 1) were evaluated, and the corresponding amine **3a** was obtained, in general, with low yields and low enantioselectivities. Though, with (*R*)-6,6'-Br_2-BINOL (**L2**) a promising 50% *ee* was observed. Then, we decided to examine vaulted ligands like (*R*)-VAPOL (**L7**) and (*R*)-VANOL (**L8**). The use of **L7** as a ligand (entry 7), afforded the product **3a** with better enantioselectivity (61% *ee*), although the yield was moderate (36%). When (*R*)-VANOL (**L8**) was used as a ligand (entry 8), **3a** was afforded in 40% yield, but almost as a racemic mixture. Subsequently, we decided to test different chiral aminoalcohols, such as quinine (**L9**) or diaryl prolinol ligands (**L10**-**L13**) used successfully in enantioselective zinc mediated reactions,[13,20] but the enantioselectivities observed were very low. Only Trost ligand[21] **L14** (entry 14) gave some asymmetric induction (20% ee). Other ligands such chiral α-hydroxyamides **L15** (entry 15) and **L16** (entry 16), developed in our research group for the addition of organozinc reagents to carbonyl compounds[22] were also evaluated, but they proved to be unsuccessful ligands in the addition of Et_2Zn to cyclic imines.

Table 1. Ligand screening.[a]



Entry	Ligand (20 mol%)	Yield (%)[b]	*ee* (%)[c]
1	**L1**	36	37
2	**L2**	34	50
3	**L3**	20	14
4	**L4**	18	19
5	**L5**	16	8
6	**L6**	22	18
7	**L7**	36	61
8	**L8**	40	5
9	**L9**	30	5
10	**L10**	47	0
11	**L11**	53	0
12	**L12**	48	1
13	**L13**	55	5
14	**L14**	48	20
15	**L15**	19	11[d]
16	**L16**	33	8

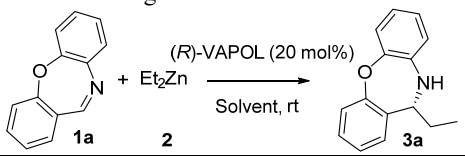
[a]Reaction conditions: **1a** (0.1 mmol), 1M Et_2Zn (**2**) in hexane (0.5 mmol) and Ligand **L** (0.02 mmol) in 2 mL of CH_2Cl_2 at room temperature for 24 hours.

[b]Isolated yield after column chromatography.

[c]Enantiomeric excess were determined by HPLC using chiral stationary phase.

[d]Opposite enantiomer was obtained.

Table 2. Solvent screening.[a]



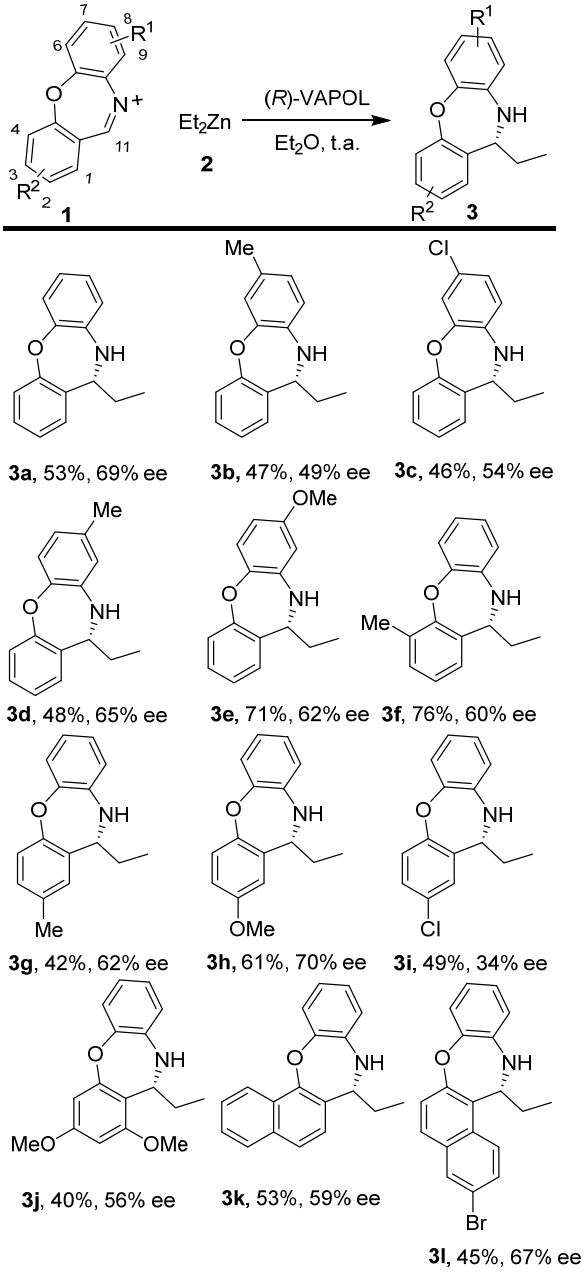
Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	CH_2Cl_2	53	61
2	$ClCH_2CH_2Cl$	68	38
3	THF	70	27
4	MTBE	52	54
5	iPr_2O	49	42
6	Et_2O	53	69
7	Toluene	49	45
8	AcOEt	58	44

[a]Reaction conditions: **1a** (0.1 mmol), 1M Et_2Zn (**2**) in hexane (0.5 mmol) and Ligand **L** (0.02 mmol) in 2 mL of solvent at room temperature for 24 hours.

[b]Isolated yield after column chromatography.

[c]Enantiomeric excess were determined by HPLC using chiral stationary phase.

With (*R*)-VAPOL (**L7**), which gave the best enantioselectivity, we decided to continue the optimization process testing different solvents (Table 2). Dichloroethane provided better conversion but lower enantiomeric excess than dichloromethane. With ethereal solvents (THF, MTBE or *i*Pr$_2$O) lower levels of enantioselectivity were obtained for compound **3a**. However, when Et$_2$O was used as a solvent an improvement in the enantiomeric excess was observed and product **3a** was afforded in 69% *ee* (Entry 5, Table 2). Other solvents such toluene or AcOEt did not improve the results obtained with Et$_2$O. Our efforts to improve the enantiomeric excess of compound **3a** were unsuccessful, therefore we decided to study the scope of the reaction with the conditions shown in entry 6, Table 2.



Scheme 2. Scope of asymmetric addition of Et$_2$Zn to dibenzo[*b*,*f*][1,4]oxazepine derivatives.

We tested several cyclic seven membered imines containing different electron-withdrawing or electron-donating groups with Et$_2$Zn. The reaction, in general, proceed with good yields (40-71%) and moderate enantioselectivities (34-70% *ee*). When the substituents are placed in 7-position (**3b**-**3c**), the conversion and the enantiomeric excess observed were lower. Whilst, when the substituents were at 8-position the enantioselectivities were around 60%. On the other hand, the electronic character of the substituents at 2-position (**3g**-**3i**) had an influence in the enantioselectivity of the reaction. For example, electron-donating groups such methoxy led to the reaction product with 70% *ee*, whilst electron-withdrawing groups such chlorine lowered the enantioselectivity of the reaction (34% *ee*). Finally, naphthyls groups were tolerated in the reaction, obtaining the corresponding alkylated amines **3k** and **3l** with moderate enantioselectivities, 59% *ee* and 67 % *ee* respectively. Our efforts to expand our methodology to other organozinc reagents were unsuccessful. When Me$_2$Zn, Bu$_2$Zn and *i*Pr$_2$Zn were tested under the optimized reaction conditions very low conversions to the corresponding alkylated products were observed.[23]

3. Conclusions

In summary, we have reported the enantioselective alkylation of dibenzo[*b*,*f*][1,4]oxazepine derivatives with Et$_2$Zn catalyzed by a (*R*)-VAPOL-Zn(II) complex. This methodology has provided an approach to synthesize optically active 11-ethyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine derivatives with good yields (up to 76%) and moderate enantioselectivities (up to 70% ee). The present study extends the scope of the catalytic asymmetric addition of organometallic reagents to cyclic seven membered imines, and represents the first enantioselective addition of Et$_2$Zn to cyclic imines.

Acknowledgments

Financial support from the MINECO (Gobierno de España; CTQ2013-47494-P) is gratefully acknowledged. L. M. thanks the Generalitat Valenciana for predoctoral grant. C.V. thanks MINECO for a JdC contract.

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23. We attribute these lack of reactivity for the other organozinc reagents (Me_2Zn, Bu_2Zn and iPr_2Zn) due to the Zn(II)-complex formed is different for each organozinc reagent, and the only reactive is the complex formed with Et_2Zn.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://. These data include complete experimental procedures and characterization of new products, ^1H and ^{13}C NMR spectra, and HPLC chromatograms.