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Enantioselective Allylation of Aldehydes Promoted by Chiral Zinc Bis(Oxazoline) Complexes

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Abstract: *In this paper we introduce a simple, new system for promoting enantioselective catalytic allylation of aldehydes. Chiral bis(oxazalinyl) zinc complexes have been shown to catalyze the allylation of aldehydes in good yield when allyl tributyltin is used as the nucleophile. The values of e.e. obtained for this reaction are in the range of 40-46%. A number of different reaction conditions were screened and the results obtained with other metal systems are also reported.*

Chiral bis(oxazoline) metal complexes[1] have been shown to catalyze a large number of reactions including cyclopropanations,[2] aziridinations,[3] and the reduction of ketones[4]. Moreover, the stoichiometric use of chiral bis(oxazoline) metal complexes for the addition of organolithium compounds,[5] allylation reactions[6] and radical reactions[7] have been described.

Recently, Corey[8] and Evans[9] demonstrated the capacity of metal bis(oxazoline) complexes to act as Lewis acids for promoting Diels-Alder reactions and Mukaiyama reactions.[10] Our group recently introduced a high enantioselective allylation methodology[11] based on BINOL-titanium and -zirconium metal complexes. In searching for other metal complexes which are able to promote this reaction with the aim of increasing the reaction rate and the possibility of utilizing stereogenic allyltin compounds, we screened a large number of metals and ligand combinations using a combinatorial approach. Through this screening process we discovered the catalytic properties of zinc oxazoline complexes in promoting the allylation of aldehydes. Herein we report the preliminary results of this straightforward methodology.

Scheme 1

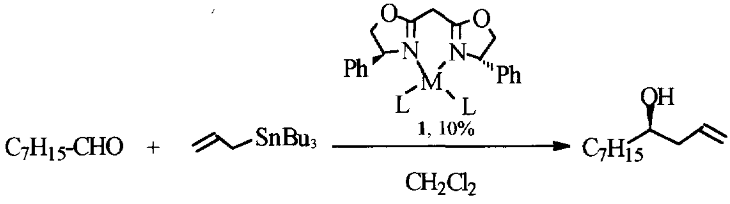


Table 1. Enantioselective allylation of octanaldehyde promoted by bis(oxazoline) metal complexes

Entry	metal salt	T (°C)	t (hours)	Yield%[a]	e.e.%[b,c]
1	FeI_2	24	24	0	-
2	MgI_2	24	24	0	-
3	$MgBr_2$	24	24	0	-
4	$InCl_3$	24	18	52	10
5	$Mg(ClO)_4$	24	18	60	0
6	$SnCl_2$	24	22	60	0
7	$Sn(OTf)_2$	24	22	46	9
8	$Cu(OTf)_2$	24	20	63	0
9	$ZnCl_2$	24	18	10	40
10	$ZnBr_2$	24	18	54	40
11	ZnI_2	24	18	78	40

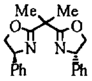
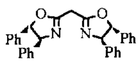
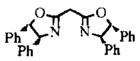
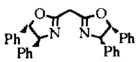
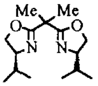
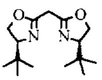
a) Isolated yield after chromatographic purification b) The enantiomeric excesses were determined by GC analysis with a chiral column. c) The (R) absolute configuration of the allylated product as determined by a comparison of the retention time of the known enantiomers on a chiral GC Megadex 5 (pentyldimethyl-β-cyclodextrin) column. Retention time (min.) 16.6 (S); 17.1 (R) at 107°C.

As a prober reaction we have chosen the allylation of octanal by allyl tributyltin (Scheme **1**) and we screened a number of metal salts using the commercially available bis(oxazoline) **1**. The results obtained are reported in Table **1**.

The combination of zinc halides and bis(oxazoline) **1** appears to smoothly and enantioselectively promote the allylation reaction (entry 9-11, Table **1**) while all the other metal salts tested fail to afford a significant enantiocontrol. This is particularly surprising in the case of copper (II) triflate (entry 8, Table **1**) since it is the metal of choice in the best catalytic systems for Diels-Alder and Mukaiyama reactions. Our next efforts were in the direction of optimizing the ligand system. In Table **2**, we report the results obtained for the reaction between octanal and allyltributyl tin with a number of different bis(oxazoline) zinc complexes.[12]

Based on our results, the following points can be established i) The yield of the homoallylic alcohols depends on the Zn salt (F<<Cl<Br<I<OTf). ii) The phenyl substituted bis(oxazolines) (entries 9-11, Table **1** and entries 3 and 4, Table **2**) give higher enantiomeric excesses. iii) The use of the bis(oxazoline) derived from 2,2-dimethylmalonate (entries 1 and 5, Table **2**) lowered the e.e. of the reaction.

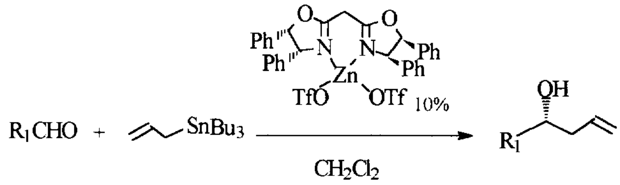
Table 2. Catalytic allylation of octanal in the presence of chiral bis(oxazoline) zinc complexes

Entry	Zinc salt	bis-(oxazoline)	T(C°)	t (hours)	Yield%[a]	e.e%.[b]
1	ZnI_2		22	18	68	23(R)
2	ZnF_2		22	25	0	-
3	$Zn(OTf)_2$		27	20	85	32(S)
4	ZnI_2		22	20	45	38(S)
5	$ZnBr_2$		22	20	35	5(R)
6	$Zn(OTf)_2$		27	18	15	14(R)

a) Isolated yield after a chromatographic purification. b) The enantiomeric excesses were determined by GC analysis with a chiral column Megadex 5.

We have also observed that the reaction can be extended to other substrates with similar results (Table **3**). This aspect is of particular concern, since metal bis(oxazoline) complexes are generally unsuccessful in promoting enantioselective reaction with non-chelating substrates, in fact the tridentate bis(oxazolinyl) pyridine are required to obtain good results in Diels-Alder reactions with methacrolein.[13] Although the exact mechanism of the reaction is obscure, preliminary studies of the zinc complex generated in deuterated solvent have shown that the formation of an allyl zinc bis(oxazoline) species can be excluded and the reaction probably proceeds via a Lewis acid-mediated pathway. Work is actually in progress in our laboratory to improve the enantiomeric excesses through the synthesis of new bis(oxazolines)[14] and the employment of different reaction conditions.

Table 3. Enantioselective allylation of aldehydes promoted by Zn(OTf)$_2$ bis(oxazoline) complex



Entry	R$_1$	T, C°	t, (hours)^a	Yield%^{b}	e.e.%^{c}
1	c-C$_6$H$_{12}$	25	9	45	46 (R)
2	Ph-CH=CH	25	9	71	34 (R)
3	Ph	25	30	80	35^d(R)

a)Yields are not optimized b) Isolated yield after a chromatographic purification. The other product in the reaction mixture was unreacted aldehyde. c) Determined by GC analysis with a chiral column Megadex 5. d) The enantiomeric excess was determined for the silylated alcohol. Retention times, min. (T, °C): R$_1$=c-C$_6$H$_{12}$ 14.5 (S), 14.8 (R) (T= 80°C); R$_1$=Ph-CH=CH 20.0 (R), 20.5 (S) (T=140°C); R$_1$=Ph 25.1 (R), 25.7 (S) (T=80°C).

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12. A typical experimental procedure follows: To a stirred solution of the bis(oxazoline) (0.1mmol) in CH$_2$Cl$_2$ (10mL), was added the zinc salt (0.1mmol) and the resulting mixture was stirred for 2 hours at room temperature. Allylstannane (1.5mmol) and the aldehyde (1 mmol) were added to this mixture and it was stirred at room temperature for 24 hours. The reaction was quenched by adding a saturated solution of NaHCO$_3$ and the organic phase was separated. The aqueous phase was extracted with Et$_2$O and the organic phases were collected, dried, and concentrated under reduced pressure to give an oil which was purified by flash chromatography (cyclohexane:Et$_2$O)
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14. Studies with other new bis-(oxazoline) prepared by the synthesis of the corresponding chiral amino-alcohol are underway in our laboratory.

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