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Cationic Bis(oxazoline) and Pyridyl-bis(oxazoline)Cu(II) and Zn(II) Lewis Acid Catalysts. A Comparative Study in Catalysis of Diels-Alder and Aldol Reactions

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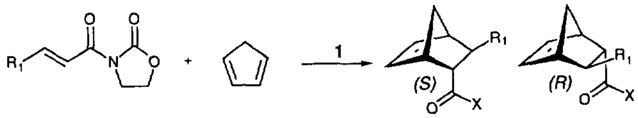
Abstract: A systematic comparison of the cationic Lewis acidic Cu(II) and Zn(II) catalysts derived from bis(oxazoline), box, and pyridyl-bis(oxazoline), pybox, ligands is presented. Upon screening the catalysts in the Diels-Alder and aldol reactions, the Cu-based catalysts were found to be superior. Copyright © 1996 Elsevier Science Ltd

We have recently documented that Cu(II) triflate complexes derived from bis(oxazoline), box, ligands are excellent chiral Lewis acids for the Diels-Alder reaction.[1] More recently, we have reported that cationic variants of these complexes and those with the related pyridyl-bis(oxazoline), pybox, ligands are even more attractive chiral catalysts for both the Diels-Alder and Lewis acid catalyzed (Mukaiyama) aldol reactions (eq 1, 2).[2,3] We have found that the cationic Cu(II)-box complex **1a** (M = Cu) is the optimal Cu-based chiral catalyst in the Diels-Alder reaction of acrylimide dienophiles (eq 1), while the cationic Cu(II)-pybox[4] complex **2a** (M = Cu, X = SbF_6) is the preferred catalyst for the aldol addition of benzyloxyacetaldehyde with a variety of enolsilanes (eq 2). What remained to be demonstrated is whether other divalent metal complexes might also provide an equally attractive platform for chiral Lewis acid design with this family of ligands. To address this issue, we have undertaken a comparison of Cu(II)- and Zn(II)-box and pybox-derived catalysts in these reactions (eq 1, 2). Zn(II) was chosen as an organizational metal center, with the intention of using the favored tetrahedral and trigonal bipyramidal geometries to complement the square planar and square pyramidal configurations observed with Cu(II).[5] In addition, the lower redox potential of Zn(II) (-0.76 V) compared to Cu(II) (0.34 V),[6] makes Zn(II)-derived catalysts attractive candidates for oxidatively sensitive systems.



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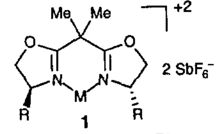

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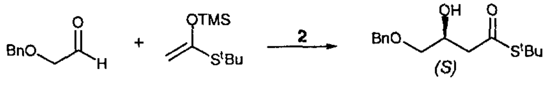
a, R = *t*-Bu ; **b**, R = Ph



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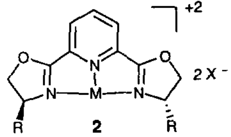

2

a, R = Ph ; **b**, R = *i*-Pr; **c**, R = Bn; **d**, R = *t*-Bu

Catalyst Preparation. The Cu(II)-box and pybox complexes **1a** (M = Cu) and **2** (M = Cu) were prepared from their respective ligand-$CuCl_2$ complexes and $AgSbF_6$ in direct analogy to the procedure previously reported by us.[2] The related zinc complexes **1b** (M = Zn) and **2** (M = Zn) were prepared in an analogous fashion using ZnI_2. For purposes of comparison, the analogous triflate complexes were prepared from the ligand and $M(OTf)_2$ according to our precedent.[1] The X-ray structures of the metal halide-(*S,S*)-box ligand complexes are shown in Figure 1. In this and related studies, we have found that the degree of distortion from square planarity for the Cu(II) complexes varies from 37° for the illustrated $CuCl_2$ complex to 24° for the analogous bis(aquo) complex.

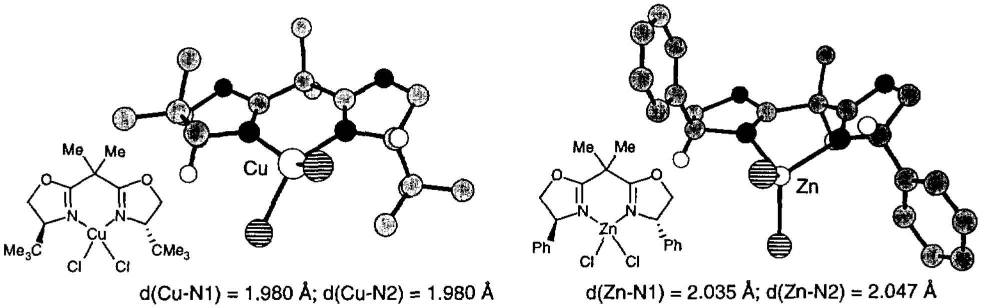

Figure 1. X-ray structures of the $CuCl_2$- and $ZnCl_2$-(*S*),(*S*)-bis(oxazoline) complexes **1**.

Diels-Alder Reaction Comparison. Given the proper ligand substituent, the Cu(II) and Zn(II) bis(oxazoline) complexes **1a** (M = Cu) and **1b** (M = Zn) are very effective catalysts for the Diels-Alder reaction of acrylimide dienophiles (eq 1). The optimal *tert*-butyl ligand-Cu(II) complex **1a** (M = Cu) afforded the (*S*) cyclopentadiene adduct in >95% yield and >98% ee (96:4 *endo:exo*, -78 °C, CH_2Cl_2, 4 h).[7,8] In contrast, the optimal catalyst system for Zn(II) is the phenyl-substituted complex **1b** (M = Zn) which affords the enantiomeric (*R*) cyclopentadiene adduct in >90% yield and 92% ee (98:2 *endo:exo*, -78 °C, CH_2Cl_2, 8 h).[9] This observation is consistent with prior studies that have demonstrated that the Mg(II)-Ph-box Lewis acid exhibits optimal asymmetric induction in this reaction (eq 1) with this ligand.[10] Qualitative observations on the two catalysts indicate that the copper complex is a more effective catalyst on the basis of both conferred enantioselection (>98% ee vs. 92% ee) and rate acceleration (4 h vs. 8 h for complete conversion).

The temperature effects on enantioselection revealed a dramatic difference between the two catalysts. While the Cu(II) catalysts are effective over a wide range of temperatures, reaction enantioselectivity falls off dramatically for the Zn(II) catalysts at higher temperatures (Figure 2).

To further probe the generality of the Zn(II)-Ph-box catalyst in this reaction, the crotonate-derived dienophile was evaluated with cyclopentadiene (eq 1, R_1 = Me) at 25 °C and was found to be only moderately enantioselective (64% ee). This result falls short of the results obtained with the Cu(II)-*tert*-Bu-box catalyst (96% ee, 25 °C). To date, box complexes derived from Fe(III)[11] and Mg(II)[10] have also been reported to catalyze the acrylimide Diels-Alder reaction (eq 1, R_1 = H). We have compared these catalysts with crotonimide dienophiles (eq 1, R_1 = Me). The performance of these catalysts is eroded with β-substituted dienophiles whose lower reactivity required higher reaction temperatures. In conclusion, we have yet to find a bis(oxazoline) metal complex that is superior to the Cu(II)-based catalysts recently reported by us.

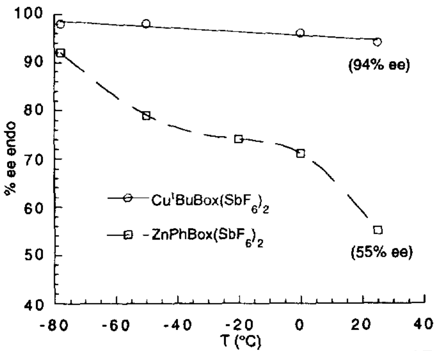

Figure 2. Enantioselectivity-temp. profile for Zn[Phbox]SbF_6 & Cu[t-Bubox]SbF_6 catalyzed Cycloaddition (eq 1, R_1 = H)

The tridentate (pybox) complexes **2a** (M = Cu, Zn, X = SbF_6) also promote enantioselective Diels-Alder reactions (eq 1, R_1 = H), with both catalysts affording the (*S*) product enantiomer. The relevant enantioselectivities and times for complete conversion for the two catalysts (10 mol%) at -78 °C are as follows: **2a**, M = Cu, 90% ee, 16 h; **2a**, M = Zn; 90% ee, 16 h. Not unexpectedly, the pybox ligand compromises the Lewis acidity of the complexes **2** relative to their bidentate counterparts which are the ligands of choice for the imide dienophiles.

The sense of asymmetric induction for both the Cu(II)box- and Zn(II)box-dienophile complexes is in accord with expectation. Each of the dienophile-catalyst complexes was computer generated with the aid of the crystallographic data presented in Figure 3.

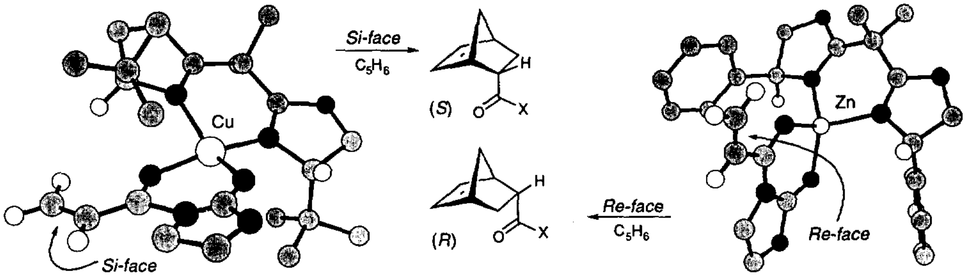

Figure 3. Computer generated structures of the **1a** (M = Cu) and **1b** (M = Zn)-dienophile complexes.

We thus conclude that the cationic Cu(II)-box complexes are superior to their Zn(II) counterparts as chiral Lewis acid catalysts for the imide Diels-Alder reaction (eq 1), particularly with β-substituted dienophiles. It is also noteworthy that the ability of the Cu(II) metal center to maintain a well-defined substrate-catalyst geometry, especially at higher temperatures, is an important attribute of this Lewis acidic metal center that is lacking in the analogous Zn(II) complexes. In a recent study on divalent metal ion catalysis in the Diels-Alder reaction in aqueous media, the relative catalytic efficiencies of Cu(2+), Zn(2+), Ni(2+), and Co(2+) were compared.[12] This investigation has also concluded that Cu(2+) is the superior metal ion for bidentate dienophilic substrates.

Aldol Reaction Comparison. The aldol reaction between the two-point binding substrate benzyloxyacetaldehyde and the *tert*-butyl thioacetate-derived silyl ketene acetal (eq 2) was also employed to evaluate the differences between Cu(II) and Zn(II) Lewis acids. Both ligand-metal complexes **1** (M = Cu, Zn) and **2** (M = Cu, Zn, X = SbF_6) will catalyze this reaction with good enantioselection. While this reaction proceeds rapidly (≤ 1 h, -78 °C, 10 mol% cat.) with the Cu(II)- and Zn(II)-box derived complexes **1**, the enantioselectivities for the best cases[13] were inferior to those observed with the pybox complexes **2a** (M = Cu, Zn, X = SbF_6). Accordingly, the pybox-M(II) complexes **2a** were employed for comparison purposes.

As previously reported, the reaction between the illustrated silylketene acetal and benzyloxyacetaldehyde (eq 2) proceeds with high enantioselectivity (99% ee) with the phenyl-pybox Cu(II) catalyst **2a** (M = Cu, X = SbF_6) (-78 °C, CH_2Cl_2, 0.5 mol% catalyst).[3] The systematic comparison of metal center (Cu vs. Zn), counterion (OTf^- vs. SbF_6^-), and ligand substituent is presented in Table 1. As the data reveal, the phenyl-pybox ligand complex **2a** and SbF_6^- counterion are the optimal constituents for both Cu(II) and Zn(II) catalysts. Two significant advantages are evident for the copper-based catalysts. The enantioselection is superior for Cu(II) (99% ee vs. 78% ee) and the reaction times are shorter (15 min vs. 4 h). Although we have not rigorously determined the origin of the rate differences for the two catalysts, the working hypothesis is that catalyst turnover could be a greater problem for the Zn(II) catalyst system. In summary, we conclude that, in the Cu/Zn comparison in the aldol reaction, the Cu(II) center is again superior to related chiral Lewis acids that might be constructed from Zn(II).

Table 1. Pyridyl-bis(oxazoline) Catalysts **2** in the Aldol Reaction (Eq 2).[a]

		M = Cu		(S)			M = Zn		(S)
entry	R	X	time[b]	% ee[c]	entry	R	X	time[b]	% ee[c]
1	**Ph**	**SbF_6**	**15 min**	**99**	**6**	**Ph**	**SbF_6**	**4h**	**78**
2	Ph	OTf	15 min	96	7	Ph	OTf	12 h	40
3	*i*-Pr	SbF_6	1 h	85	8	*i*-Pr	SbF_6	1 h	36
4	Bn	SbF_6	3 h	67	9	Bn	SbF_6	1 h	40
5	*t*-Bu	SbF_6	8 h	9	10	*t*-Bu	SbF_6	15 min	18

a) Reactions were carried out in CH_2Cl_2 (0.2 M in substrate, 10 mol% cat., -78 °C). b) Reaction times for complete conversion. c) Enantiomer ratios assayed by chiral HPLC with a Daicel ODH column.

The Ph-pybox-Cu(II) and -Zn(II) complexes **2a** afford the same sense of induction in the aldol reaction. Both systems appear to carry the requirement of internal chelation for high levels of asymmetric induction. For the copper catalyst, the intervention of a square pyramidal catalyst-substrate complex is in accord with the observed sense of induction if the aldehyde carbonyl oxygen is complexed in the stronger-binding equatorial plane. The ESR spectrum of this complex also supports a square pyramidal geometry.[3] The computer-generated representation of the methoxyacetaldehyde-Cu[Ph-pybox](II) complex provided in Figure 4 clearly indicates the greater accessibility of the *si*-face of the coordinated aldehyde carbonyl moiety. One can only speculate on the geometry of the analogous aldehyde-Zn[Ph-pybox](II) complex; however, it is reasonable that a trigonal bipyramidal geometry might be expected.[14]

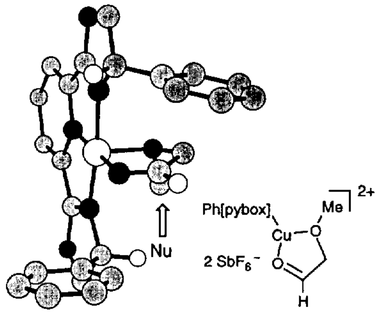

Figure 4. Square pyramidal Cu(II)[Ph-pybox]-methoxyacetaldehyde complex.

In conclusion, we have defined the optimal ligand environments for four- and five-coordinate Cu(II) and Zn(II) complexes with bis(oxazoline) and pyridyl-bis(oxazoline) ligands in Diels-Alder and Mukaiyama aldol reactions. In general, good levels of induction can be achieved with both metals, although the apparent ability of the Cu(II) metal center to maintain a well-defined substrate-catalyst geometry, especially at higher temperatures, is a real attribute of this Lewis acidic metal center that is lacking in the analogous Zn(II) complexes. Finally, the Lewis acidity of the Zn(II) is less than Cu(II) as gauged by the Diels-Alder reaction, particularly with β-substituted dienophiles.

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7) Enantioselection as a function of the Cu(II)-box substituent R at -78 °C is as follows: R = CMe_3, >98%; R = $CHMe_2$, 58%; R = Ph, 30%. For the details of running these reactions see ref 1 and 2.
8) All reactions were carried out in CH_2Cl_2, 0.2 M in dienophile and 5 equiv of diene with 10 mol% of catalyst. Enantiomer ratios were determined by chiral HPLC using a Daicel ODH column.
9) Enantioselection as a function of the Zn(II)-box substituent R at -78 °C is as follows: R = CMe_3, 56%; R = $CHMe_2$, 53%; R = Ph, 92%.
10) (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807-6810. (b) Desimoni, G.; Faita, G.; Righetti, R. P. *Tetrahedron Lett.* **1996**, *37*, 3027-3030. The bias for the phenyl substituent with metals that coordinate in a tetrahedral geometry could result from both steric and electronic effects. Possible contributions from electronic effects have not yet been addressed.
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13) The best cases for the bis(oxazoline) ligands were as follows: *tert*-Bu-bis(oxazoline)Cu$(OTf)_2$, 91% ee, *(R)* configuration; phenyl-bis(oxazoline)Zn$(SbF_6)_2$, 85% ee, (*S*) configuration.
14) The related Cu(II) and Zn(II) complexes of the tridentate ligand 2,6-diacetylpyridyl dioxime are square pyramidal and trigonal pyramidal respectively. Nicholson, G. A.; Petersen, J. L.; McCormick, B. J. *Inorg. Chem.* **1982**, *21*, 3274-3280.

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