

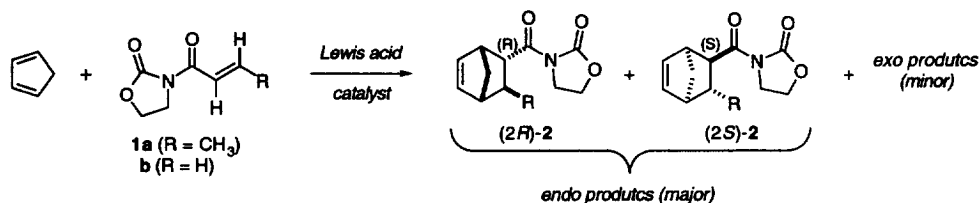
Enantioselective Diels–Alder reactions: room temperature bis(oxazoline)-zinc, -magnesium, and -copper triflate catalysts

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Abstract: A series of chiral bis(oxazoline) ligands, differing in the length of the chain connecting the chiral oxazoline subunits and in the nature of the substituent at the chiral center, were examined in the room temperature Zn(OTf)₂, Mg(OTf)₂ and Cu(OTf)₂ catalyzed reaction of N-crotonyloxazolidinone with cyclopentadiene. A 1,4-bis(oxazoline) ligand proved best for Zn(OTf)₂ and afforded product consistent with reaction via an octahedral model, while 1,3-bis(oxazoline) ligands were best for Mg(OTf)₂ and Cu(OTf)₂.
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We have been interested in the use of chiral bis(oxazoline) ligands (box ligands) for certain iron,¹ rhodium,² and palladium-catalyzed³ carbocyclizations, and having access to these ligands, became interested in the use of their metal complexes in Lewis acid catalyzed reactions.⁴ The Lewis acid catalyzed Diels–Alder reaction provides a useful venue for testing approaches to the design of asymmetric catalysts, and in particular, the reactions of α,β -unsaturated N-acyloxazolidinones (e.g., **1**) provide a useful standard for testing the efficacy of two point binding chiral Lewis acids. Several notable successes have been achieved in the Diels–Alder reactions of **1** and closely related substrates, particularly using C₂-symmetric chiral box ligands in conjunction with copper(II),^{5–12} magnesium(II),^{11,13,14} and iron(III) salts.^{11,12,15}



Zinc(II) salts constitute useful reagents for Lewis acid catalyzed transformations in organic synthesis, and at the onset of our studies, their absence from among the very successful chiral Lewis acid catalysts was surprising.⁵ Furthermore, while a number of very efficient catalyst systems had been defined that afford very high enantiomeric excess at low to very low temperature, efficient catalysts that operate at higher temperatures could have practical implications for large scale reactions and perhaps in regard to substrate scope. We therefore set as a goal to look for efficient catalysts that operate at or near ambient temperature, with particular emphasis on finding an efficient chiral bis(oxazoline)Zn(II)-catalyst system.

We reasoned that different metal salts should demand different optimal distances separating the two oxazoline moieties to accommodate intrinsic differences in ionic radii and/or coordination geometry. To test this hypothesis, chiral bis(oxazoline) ligands **3**,¹⁶ **4**,¹⁷ and **5**¹⁸ (1,2-, 1,3- and 1,4-box ligands, respectively; R¹ = CH₂Ph, CHPh₂, Ph, *t*-Bu) were synthesized via the standard methods and screened in combination with Zn, Mg, and Cu salts as catalysts for the cycloaddition of cyclopentadiene with the

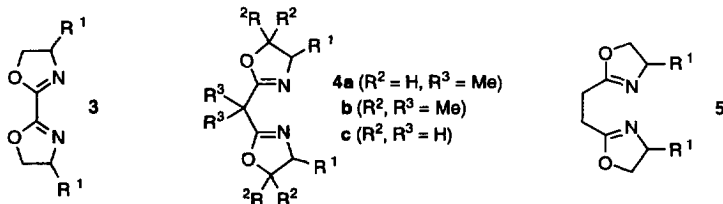
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Table 1. Room temperature [(box)M(OTf)₂]-catalyzed cycloadditions of **1a** with cyclopentadiene^a

R ¹ -ligand ^b	Mg(OTf) ₂			Zn(OTf) ₂			Cu(OTf) ₂		
	% yield	endo:exo	% ee ^c	% yield	endo:exo	% ee ^c	% yield	endo:exo	% ee ^c
Bzl-3 (S)	10	7.6	nr	99	5.1	nr	91	6.5	20 (S)
Ph-3 (S)	30	6.0	nr	99	6.3	nr	90	9.7	nr
<i>t</i> -Bu-3 (S)	13	4.4	6 (R)	99	7.1	10 (S)	99	10.6	17 (S)
Bzl-4a (S)	99	3.5	12 (R)	99	6.9	14 (R)	99	9.7	8 (S)
Ph-4a (R)	99	3.2	73 (R)	99	8.5	32 (R)	99	8.7	22 (R)
Ph-4b (S)	95	2.5	87 (S)	98	4.4	12 (S)	60	1.6	nr
<i>t</i> -Bu-4a (S)	21	4.7	nr	80	5.5	nr	90	6.7	76 (S)
<i>t</i> -Bu-4c (S)	28	3.6	nr	99	6.2	10 (R)	99	5.8	8 (S)
Bzl-5 (R)	44	3.0	14 (S)	72	5.0	nr	92	1.5	nr
Ph ₂ C(H)-5 (R)	21	3.8	nr	89	2.3	12 (S)	75	4.0	nr
Ph-5 (R)	16	8.7	20 (R)	98	8.0	72 (R)	99	2.7	51 (R)
Ph-5 (S)	15	7.4	17 (S)	99	8.0	78 (S)	90	2.6	51 (S)
<i>t</i> -Bu-5 (S)	40	3.0	12 (S)	81	4.5	14 (S)	99	3.4	nr

a) All reactions were run using a mixture of 0.2 equiv. M(OTf)₂, 0.22 equiv. bis(oxazoline), and 0.5 mmol of **1a** in dichloromethane (ca. 0.1 M in **1a**, 25 °C), and after allowing that mixture to equilibrate for ca. 30 min, 6 mmol of cyclopentadiene was added. Reactions were run until **1a** was completely consumed up to a limit of 24 h. b) The absolute configuration of the oxazoline is indicated in parentheses. c) The percent enantiomeric excess of the endo isomer is determined by chiral HPLC (Chiral Technologies, Inc. Chiralcel OD column, 95:5 hexane:isopropanol) or GC (J&W Scientific CDX-B column) analysis; nr = near racemic. The absolute configuration of the 2-position in product **2** is indicated in parentheses.

N-crotonyloxazolidinone **1a**. At the onset, we decided to screen metal triflates based on the assumption, in retrospect likely a faulty assumption (*vide infra*),⁶ that the triflate counterion would dissociate to afford strongly Lewis acidic [(box)M²⁺]-catalysts.



Initially, one might assume that an optimal low temperature catalyst would constitute the optimal catalyst at higher temperatures as well, but given the multiple equilibria involved in typical chiral Lewis acid catalyzed reactions,¹⁹ this need not be the case. For example, data recently reported by Evans⁵ shows that the temperature dependence of enantioselectivity is vastly different for two similar [(1,3-box)M(SbF₆)₂]-catalysts (M=Cu, Zn). We observed similar results in the course of our studies. Therefore, all reactions reported in Table 1 were run at room temperature. The relative reactivities of the various [(box)M(OTf)₂] combinations generally follow the order: Cu(OTf)₂ faster than Zn(OTf)₂ faster than Mg(OTf)₂. In the case of Mg(OTf)₂, only two of the box ligands, the 1,3-box ligands **4a** (R¹=CH₂Ph, Ph) and **4b** (R¹=Ph), gave catalysts that effected complete conversion within a 24 h reaction period. The endo selectivity of the various catalysts varies widely, affording endo:exo ratios from 1.5 to greater than 10 to 1.

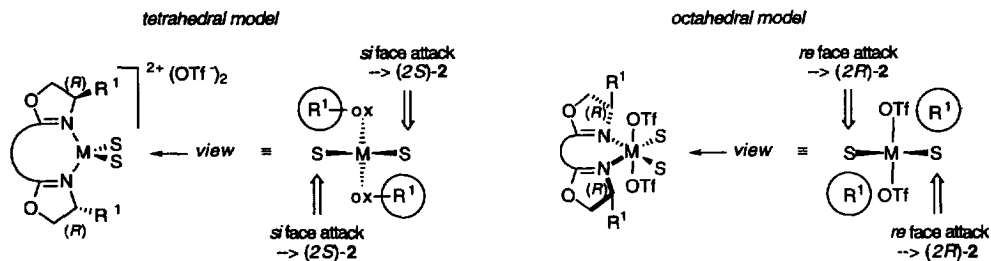


Figure 1. Tetrahedral and octahedral models for the [(box)M(OTf)₂]-catalyzed Diels–Alder cycloaddition of **1** with cyclopentadiene (S=chelated dienophile **1** assuming the *s*-cis conformation).

Enantioselectivities up to 87% ee are observed, and it should be recognized that none of the reactions were optimized. In accord with our initial expectations, different metal salts demand different optimal distances separating the two oxazoline moieties. The best Zn(OTf)₂ catalyst is derived from the 1,4-box ligand **5** (R¹=Ph, 72–78% ee). The strong dependence on the nature of oxazoline substituent R¹ is striking.²⁰ While the phenyl-substituted [(**5**)Zn(OTf)₂]-catalyst affords 72–78% ee, the benzyl-, diphenylmethyl-, and *tert*-butyl-derivatives impart little asymmetric induction.²¹ In contrast to Zn(OTf)₂, the 1,3-box ligands **4a** and **4b** (R¹=Ph, 73 and 87% ee, respectively) afford the best catalysts with Mg(OTf)₂, although in both cases the endo:exo selectivity is only modest. As expected from the literature,^{5,6} the 1,3-box ligand **4a** (R¹=*t*-Bu) afforded the best catalyst with Cu(OTf)₂.

The sense of asymmetric induction observed in the [(box)Mg(OTf)₂] and [(box)Zn(OTf)₂]-catalyzed reactions is surprising. A tetrahedral model for the activated complex between (box)M²⁺ and dienophile **1a** predicts that box ligands of the R absolute configuration should leave quadrants leading to addition to the *si* face of a chelated cisoid N-crotonyloxazolidinone **1a** unencumbered (Figure 1). Such a model predicts the formation of (2*S*)-**2a** from box ligands of the R absolute configuration. Corey ascribed the selective formation of (2*S*)-**2b** in the [(*R*)-**4b** (R¹=Ph)-MgI₂/AgSbF₆]-catalyzed reaction of N-acroyloxazolidinone **1b** with cyclopentadiene to reaction via a tetrahedral (box)Mg²⁺ complex.¹⁴ Similarly, the results obtained by Evans using the [**4a** (R¹=Ph)Zn(SbF₆)₂]-catalyst are rationalized by such a model.⁵ We find that neither the Mg(OTf)₂ nor the Zn(OTf)₂-derived catalysts fit the prediction of the tetrahedral model; specifically, (*R*)-box ligands afford predominantly (2*R*)-**2a** and *S* afford (2*S*)-**2a**. The tetrahedral model predicts the opposite result.

A number of explanations could account for the observed sense of asymmetric induction. One of the simplest assumes that triflate does not dissociate under the conditions employed and the reaction proceeds via something approaching an octahedral, rather than a tetrahedral, complex. Such a model (Figure 1) predicts that the least sterically encumbered octants are those leading to approach of the diene to the *re* face of a chelated cisoid dienophile. We note that Desimoni^{12,13} proposed a conceptually similar model to account for the effect of added water in the [**4a** (R¹=Ph)Mg(ClO₄)₂]-catalyzed reaction of N-acroyloxazolidinone **1b** with cyclopentadiene, as do Sibi and Porter in their recently published enantioselective conjugate radical additions.²² Evans had earlier suggested that triflate does not completely dissociate in related Cu(II) complexes.⁶

The [(*R*) **5** (R¹=Ph)Zn(OTf)₂]-catalyzed reaction of N-acroyloxazolidinone **1b** with cyclopentadiene affords similar results to those observed with **1a**. The room temperature reaction affords cycloadduct (*R*)-**2b** (98% yield, 74% ee, endo:exo=10:1). It is interesting that the endo:exo ratio, but not the enantioselectivity, is rather sensitive to temperature effects. The same reaction carried out at –78°C gives higher endo selectivity (endo:exo=38:1), but almost no change in the enantiomeric excess (78% ee, 90% yield).

In summary, series of chiral 1,2-, 1,3- and 1,4-box ligands were examined in the room temperature Zn(OTf)₂, Mg(OTf)₂ and Cu(OTf)₂ catalyzed reactions of **1a** with cyclopentadiene. The results confirm that different metal salts demand different optimal distances separating the two oxazoline moieties and

suggest that triflate is associated in these Zn(II) and Mg(II)-complexes. The best Zn(OTf)₂ catalyst is derived from a 1,4-box ligand. On the basis of that lead, several conformationally constrained 1,4-box ligands were prepared in our labs, and the results of their [(1,4-box)M(OTf)₂]-catalyzed reactions are described in the following paper.

Experimental section

General procedures

Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen, all reactions were run at ambient temperature, all temperatures were measured externally, and all temperatures were reported in degrees Celsius (°C). The 1,2-box,¹⁶ 1,3-box,¹⁷ and 1,4-box¹⁸ ligands were either purchased or prepared by literature methods. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl prior to use. Hexanes (Hex) were purified by distillation. Dichloromethane (DCM) was passed through a column of alumina. All other reagents and solvents received from commercial sources were used without further purification. Melting points are uncorrected. Optical rotations were measured using 10 cm cells on a Rudolph Autopol III polarimeter at ambient temperature. Thin layer chromatographic (TLC) analyses were performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized by using a hand-held short wavelength ultra-violet lamp (254 nm) or iodine chamber. All ¹H and ¹³C NMR spectra were obtained on a GE Omega 300 or 500 MHz spectrometer. Unless otherwise noted, all NMR spectra were obtained on solutions in CDCl₃. All ¹H spectral data are reported in ppm from an internal standard tetramethylsilane or residual chloroform as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (reported in Hertz) and integration. All ¹³C NMR spectra were decoupled with waltz-16 decoupling. For most compounds, the number of attached hydrogens were determined using the DEPT pulse sequence. All ¹³C spectral data (s=no attached hydrogens, d=CH, t=CH₂, q=CH₃) were reported in ppm from an internal standard CDCl₃ unless otherwise noted. Infrared (IR) spectra were obtained on a Analect RFX-65 FT-IR spectrophotometer using salt plates for the attenuated total reflectance technique (ATR, neat, ZnSe crystal). Selected absorptions were reported in wavenumber (cm⁻¹). Analytical samples were purified by chromatography on silica or recrystallization followed by a high-vacuum drying pistol over P₂O₅. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

Preparation of the 1,4-box ligand Ph-5 (S)¹⁸

Zinc chloride (0.48 g, 3.6 mmol, 0.16 equiv) was fused under high vacuum. Chlorobenzene (30 mL), succinonitrile (0.75 g, 9.4 mmol, 0.43 eq.), and (S)-phenylglycinol (3.0 g, 22 mmol, 1 eq.) were added to the freshly fused zinc chloride, and the mixture was heated to reflux overnight. The chlorobenzene was removed *in vacuo*, and the residue was redissolved in CHCl₃. The solution was washed with 1 N aq NaHCO₃ and the organic layer dried over Na₂CO₃ and Na₂SO₄. The solution was concentrated to give a yellow oil which crystallized on standing: mp 96–98°C; [α]_D²⁰ = -87° (c 1.85, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.25 (m, 10 H), 5.19 (apparent t, J = 9.8, 2 H), 4.62 (dd, J = 8.7, 10.3, 2 H), 4.09 (t, J = 8.1, 2 H), 2.85 (br s, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 168.1 (s), 143.0 (s), 129.3 (d), 128.1 (d), 127.2 (d), 75.4 (t), 70.3 (t), 25.2 (t); IR (thin film, NaCl) 1666 cm⁻¹; Combustion analysis (C₂₀H₂₀N₂O₂ = 74.98% C, 6.29% H, 8.74% N) found 75.17% C, 6.40% H, 8.92% N.

General procedure for [(box)M(OTf)₂]-catalyzed Diels–Alder reactions

The metal triflate salts were weighed out in tared vials in a dry box under N₂. The loaded vials were removed from the dry box, a magnetic stirbar was added, and the vial was fitted with a rubber septum and nitrogen bubbler. An equal molar equivalent of the appropriate box ligand was then added as a solution in dry CH₂Cl₂ (approximately 50 mg/mL concentration), and the mixture was stirred at RT for 30–50 minutes. A solution of the appropriate N-acyl oxazolidinone (approximately 100 mg/mL in CH₂Cl₂) was then added and the mixture stirred at RT for an additional 20–40 minutes. Afterwards,

cyclopentadiene was added and the reactions were run until the N-acyloxazolidinone was completely consumed up to a limit of 24 h. The reaction was quenched by the addition of 1N aq NaHCO₃ (ca 1 mL) and extracted with additional CH₂Cl₂. The organic layer was separated, dried (MgSO₄), and concentrated. The percent conversion and endo:exo ratio were determined by ¹H NMR analysis of the residue. The percent enantiomeric excess of the endo isomer was determined by chiral HPLC analysis (Chiral Technologies, Inc. Chiracel OD column, 95:5 hexane:isopropanol) of the crude material, or alternatively, by chiral GC analysis (30 m J&W Scientific CDX-B column) after isolation of the endo products via column chromatography on silica.

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