

Chiral Bis(oxazoline)copper(II) Complexes as Lewis Acid Catalysts for the Enantioselective Diels–Alder Reaction

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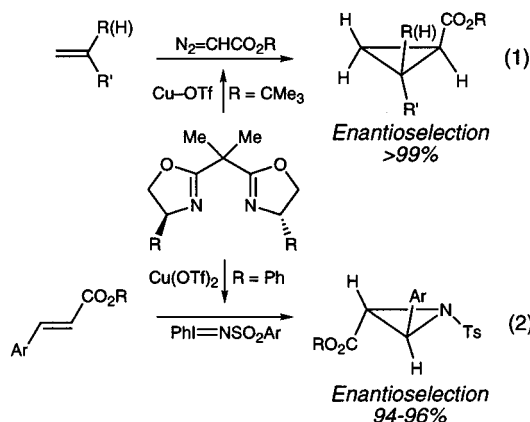
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Received April 14, 1999

Abstract: Bis(oxazoline)copper(II) complexes are highly enantioselective catalysts in Diels–Alder reactions involving bidentate dienophiles. Cationic [Cu((*S,S*)-*t*-Bu-box)]X₂ complexes with different counterions have been used as catalysts, revealing a profound influence of the counterion on the rate and stereoselectivity of the catalyst. A square-planar catalyst–substrate complex is proposed to account for the high diastereo- and enantioselectivities observed. Three bis(oxazoline)–Cu(II) X-ray structures have been obtained that support this model. Double-stereodifferentiating experiments, performed employing chiral dienophiles, afforded results that are fully consistent with the proposed square-planar transition-state assemblage. In addition to imide-based substrates, α,β -unsaturated thiazolidine-2-thiones have been introduced as a new class of dienophiles with enhanced reactivity. Kinetics experiments were performed to quantify the role that product inhibition plays in the course of the reaction. Rate and equilibrium binding constants of various catalyst inhibitors were also derived from the kinetic analysis. A comparative study was undertaken to elucidate the differences between the bis(oxazoline)–Cu(II) catalyst and the bis(oxazoline) catalysts derived from Fe(III), Mg(II), and Zn(II). Catalyst performance was found to be a function of a subtle relationship between bis(oxazoline) structure and transition metal.

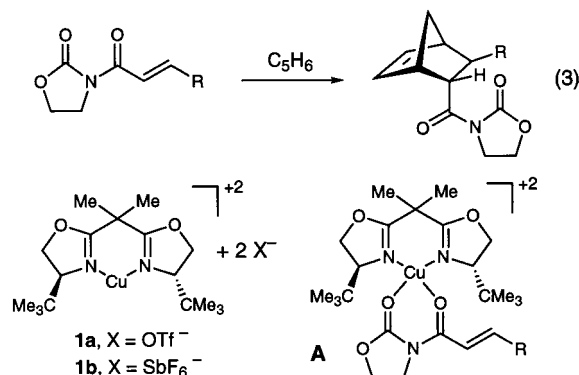
Introduction

Prior studies from this laboratory have demonstrated the utility of chiral copper complexes in asymmetric catalysis. For example, C₂-symmetric bis(oxazoline) (box)-derived Cu(I) and Cu(II) complexes have proven to be excellent catalysts for enantioselective group-transfer processes such as cyclopropanation (eq 1)² and aziridination (eq 2).³



As an outgrowth of these investigations, we have undertaken an in-depth evaluation of the potential of these and related Cu-

(II) complexes as chiral Lewis acid catalysts in the Diels–Alder reaction⁴ with imide dienophiles (eq 3). Our preliminary communications of this reaction indicate that (a) [Cu(box)]-(OTf)₂ and related complexes are excellent catalysts for this reaction⁵ and (b) the importance of catalyst counterions in modulating Lewis acidity is significant.⁶ For example, cationic [Cu(box)](SbF₆)₂ complexes exhibit both 20-fold greater reactivity and superior enantioselection than their triflate counterparts.



In this study, a detailed investigation of [Cu((*S,S*)-*t*-Bu-box)]-(X)₂ complexes **1** as chiral Lewis acid catalysts in Diels–Alder

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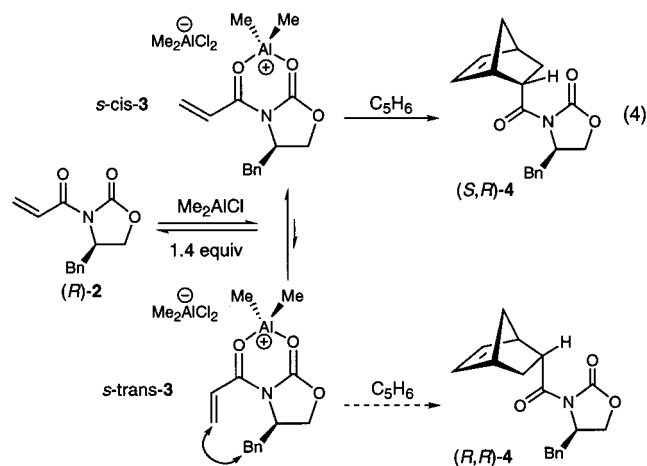
reactions of chelating dienophiles is presented. These complexes are characterized by X-ray crystallography, and a kinetics study has been employed to evaluate the extent of product inhibition. In addition, double-stereodifferentiating reactions have been carried out to assess the torsional stability of the catalyst–dienophile complex (cf. **A**, eq 3).

Auxiliary-Based Reactions. Chiral α,β -unsaturated *N*-acyloxazolidinones such as (*R*)-**2**, introduced by us in 1984, have proven to be effective dienophiles in Lewis acid-promoted Diels–Alder reactions (Scheme 1).^{7,8} These dienophiles offer the advantages of high reactivity (>100-fold that of an equivalent ester dienophile) and a well-organized dienophile–Lewis acid complex.^{7a} The stereochemical outcome of diene cycloadditions with this dienophile is consistent with (a) the intervention of a bidentate Lewis acid–dienophile complex, *s-cis*-/*s-trans*-**3** and (b) subsequent cycloaddition out of the more stable *s-cis* conformation from the more accessible dienophile diastereoface to afford the principal cycloadduct (*S,R*)-**4**. Castellino has investigated the solution structures of the Me₂AlCl and SnCl₄ complexes of these imide-derived dienophiles by ¹H NMR spectroscopy and has concluded that two-point binding is occurring with both of the indicated Lewis acids.⁹ Furthermore, an analysis of nonbonding interactions in the dienophile–Lewis acid complex suggests that the *s-cis* conformer of **3** would be expected to be more stable.¹⁰ In addition to the preceding evidence, the recently reported X-ray structures of Ti(IV) imide complexes¹¹ support our original design premise that two-point chelation between strongly Lewis acidic metal centers and this family of dienophiles is possible and that the dienophile–Lewis acid complex adopts the *s-cis* conformation in the solid state. *It is significant to the subsequent discussion that, if two-point catalyst–dienophile binding is occurring in these reactions, then the s-cis dienophile conformation must be invoked to account for the stereochemical outcome of the cycloaddition.* In fact, all published Diels–Alder reactions with this family of chiral dienophiles conform to the stereochemical predictions that follow from a diastereofacial analysis of the metal-complexed *s-cis*-**3** conformer.^{7,8}

It is on the basis of these investigations that the use of unsaturated oxazolidinone-derived dienophiles has been subsequently explored by ourselves and others in Diels–Alder reactions with chiral Lewis acid catalysts (vide infra).

Chiral Lewis Acid-Catalyzed Reactions. Complexes derived from a range of metals [Fe(III), Mg(II), Ti(IV), Yb(III), Zr(IV), Al(III), Ni(II), Cu(II)] and chiral ligands have now been reported for the Diels–Alder reactions of imide **5** (Figure 1).¹² Corey and co-workers have reported catalysts derived from bis-(oxazoline) complexes of Fe(III) and Mg(II) (**B** and **C**) in

Scheme 1



reactions of cyclopentadiene with unsubstituted dienophile **5** (R = H).^{13,14} Other important contributions from Corey's laboratory described the use of aluminum–stien complex **D** for enantioselective Diels–Alder reactions of imides.¹⁵ Narasaka has reported the effective chiral Ti(IV) catalyst **E** (R = Ph) that exhibits moderate to excellent selectivities with substituted as well as unsubstituted dienophiles **5** (R = H, alkyl).^{16,17} More recently, Kobayashi found that the chiral BINOL–Yb(III) catalyst **F** (X = OH) effectively catalyzes the reaction of **5** (R = H, alkyl) with cyclopentadiene at 0 °C with excellent levels of stereocontrol.¹⁸ An extension of that study using a bis-(acylamino)binaphthalene ligand and Yb(OTf)₃ (**F**, X = NH-COR) has been recently disclosed by Nakagawa.¹⁹ Collins has

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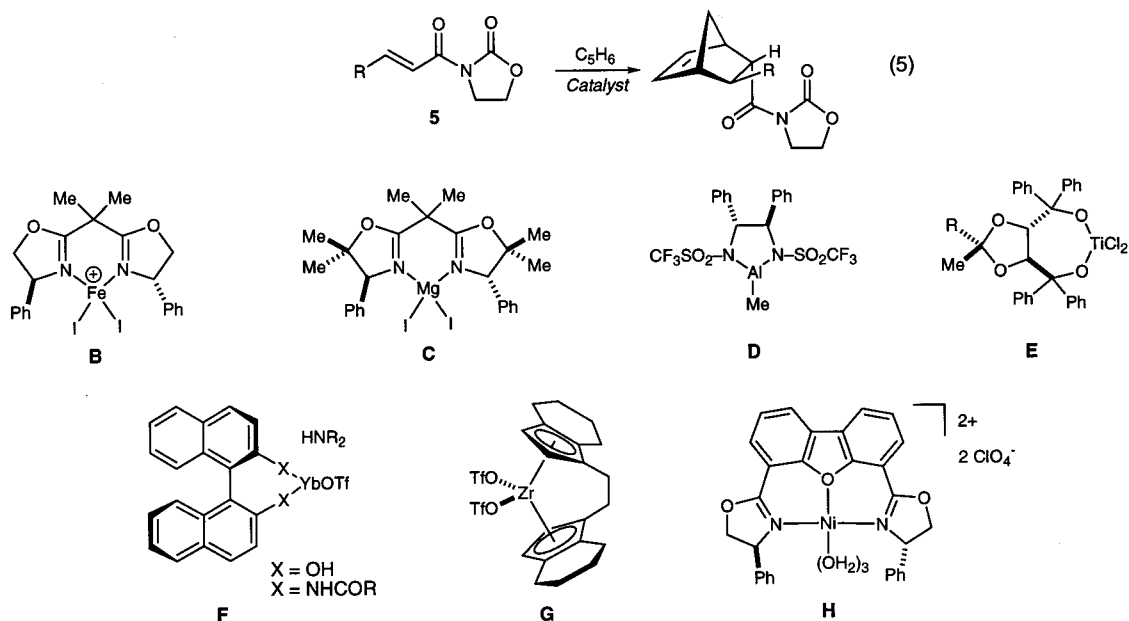


Figure 1. Complementary Diels–Alder catalyst systems.

demonstrated that $[\text{Zr}(\text{EBTHI})(\text{OTf})_2]$ (**G**) is also effective in this class of reactions; NMR studies indicate that the catalyst-bound imide adopts an *s-cis* conformation.²⁰ The successful use of hydrated nickel complex **H** as an enantioselective catalyst for cycloadditions of substituted and unsubstituted dienophiles **5** has been recently reported by Kanemasa.²¹ With catalysts **B**, **C**, and **E–H**, imide dienophile **5** presumably participates in two-point binding, although with notable exceptions, the actual structures of these complexes have not been determined. One metal–ligand complex that has been characterized by X-ray crystallography is aluminum complex **D**, which has been proposed to catalyze the illustrated reaction (eq 5) by one-point substrate binding through the *s-trans* conformation. Another solid-state characterization was provided by the Kanemasa group for the Ni(II) complex **H**. In addition, Jørgensen has reported the X-ray structure of the dienophile Ti(IV) complex formed between **D** ($R = \text{Me}$) and **5** ($R = \text{Ph}$).^{11a}

Since our initial communications describing the utility of chiral Cu(II) complexes as enantioselective Diels–Alder catalysts, a number of chiral ligands conjugated with Cu(II) salts have been evaluated as catalysts for the same reaction (Figure 2).²² Davies has employed a spiro bis(oxazoline) template (**I**, $R = -\text{CH}_2\text{CH}_2-$, $n = 0$) derived from aminoindanol for

reactions of **5** ($R = \text{H}$),²³ while Ghosh has shown the utility of the hydrated unsubstituted variant (**I**, $R = \text{H}$, $n = 4$) in reactions with several dienophiles (**5**, $R = \text{H}$, Me , CO_2Et).²⁴ Helmchen has also found that copper complexes derived from mixed phosphino–oxazoline ligands (**J**) are efficient Diels–Alder catalysts.²⁵ Finally, a new quinoline-derived copper complex (**K**) has provided good levels of enantioselectivity in one imide-based Diels–Alder reaction.²⁶

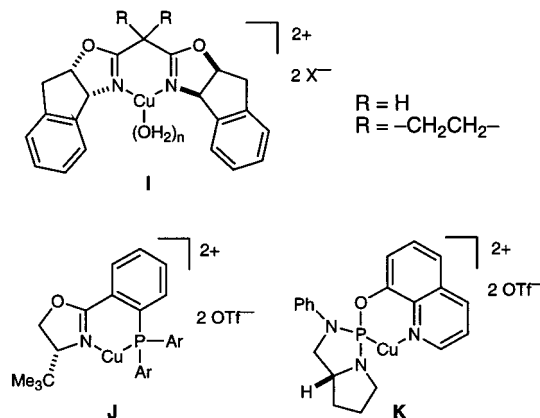


Figure 2. Cu(II)-based Diels–Alder catalyst systems.

With each of the illustrated catalysts, the interpretation of the sense of asymmetric induction has been complicated by a number of reaction variables: catalyst architecture, one- versus two-point catalyst–dienophile binding, *s-cis* versus *s-trans*

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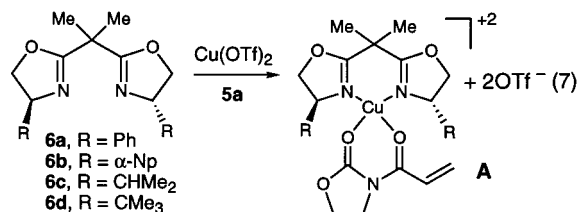
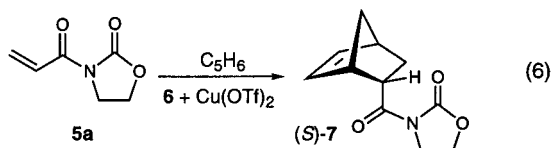
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dienophile conformation, and metal ion coordination architecture have remained largely undefined. In the following discussion, the details of our development of a practical Cu(II) Lewis acid catalyst for imide-based Diels–Alder reactions are presented.

Results and Discussion

Catalyst Development. Our initial evaluation of Cu(II)–bis(oxazoline) complexes as chiral Lewis acid catalysts was based on the reaction of acrylate imide **5a** with cyclopentadiene in the presence of complexes derived from Cu(OTf)₂ and bis(oxazoline)²⁷ ligands **6** possessing the (*S,S*) configuration (eq 6). The triflate counterion was chosen with the expectation that the bidentate dienophile would successively displace these poorly coordinating ligands to give a cationic 1:1:1-complex between ligand, Cu(2+), and dienophile, as illustrated in complex **A** (eq 7). Based on the well-established coordination chemistry of Cu(II), we anticipated a square-planar geometry for this ternary complex if both triflate counterions were dissociated.²⁸ On the other hand, the intervention of five-coordinate ternary monocationic complexes was not discounted.



Catalysts were prepared by stirring a solution of ligand **6** (1.1–1.2 equiv relative to Cu) and Cu(OTf)₂ (typically 10 mol %, ~0.03 M in catalyst) in CH₂Cl₂ at room temperature for 2–3 h. At this point, the resulting homogeneous green solution was cooled to –78 °C for the execution of the cycloaddition reaction.²⁹ Ligand–metal complexation time was found to be critical to the efficacy of the process; when the reaction was performed after only a 30-min catalyst aging time, irreproducible results characterized by the formation of nearly racemic cycloadducts with low diastereoselectivity were obtained. In contrast, when complexation was allowed to occur for longer periods (2 h or longer), the cycloadducts were obtained with uniformly high selectivities.

[Cu(box)](OTf)₂ complexes derived from ligands **6a–d**³⁰ were screened for their ability to catalyze the reaction of imide

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(29) Interestingly, in some cases the color of the catalyst was found to be thermochromic. For example, at room temperature, the catalyst solution was bright green, while at –78 °C it had changed color to blue. Workup of the reaction involved simple dilution with 5 mL of 1:1 ethyl acetate/hexane, followed by filtration through a short plug of silica. This effectively removes all Cu salts, and the product can then be analyzed. See Experimental Section (Supporting Information) for details.

(30) The syntheses of ligands **6a**, **6c**, and **6d** may be found in the supplementary material of ref 2a.

Table 1. Reaction of Imide **5a** with Cyclopentadiene Catalyzed by [Cu(box)](OTf)₂ Complexes (Eq 6)^a

ligand (R)	time, h (T, °C)	endo/exo ^b	endo ee (<i>S</i>)-7 ^b	yield (%) ^c
6a (Ph)	1 (–78), 3 (–50)	95:5	30	92
6b (α -Np)	1 (–78), 3 (–50)	94:6	44	92
6c (<i>i</i> -Pr)	1 (–78), 3 (–50)	96:4	58	93
6d (<i>t</i> -Bu)	10 (–78)	98:2	>98	86

^a Reactions were run in CH₂Cl₂ with 11 mol % ligand and 10 mol % Cu(OTf)₂. ^b Endo/exo ratios were determined by ¹H NMR and/or chiral GLC or HPLC. Enantiomer ratios were determined by chiral GLC or chiral HPLC. ^c Values refer to isolated yields of cycloadducts.

5a with cyclopentadiene (CH₂Cl₂, –78 °C, Table 1). When the (*S*)-phenylglycine-derived bis(oxazoline) **6a**–Cu(OTf)₂ complex was employed, a highly diastereoselective reaction was observed, affording cycloadducts with >20:1 endo/exo selectivity. Although the enantiomeric excess of the major endo product was low (30% ee), it was evident that the **6a**–Cu(OTf)₂ complex was functioning as a catalyst for the reaction. An evaluation of the size of the ligand substituent, R, as a function of reaction enantioselection revealed that the *tert*-butyl-substituted ligand **6d** was optimal. In reactions catalyzed by **6d**–Cu(OTf)₂ complex **1a**, the minor enantiomer of the endo product was not detected, while high endo/exo diastereoselectivity was retained (98:2). The absolute configuration of Diels–Alder adduct (*S*)-7 was determined by conversion to the derived benzyl ester, whose rotation was compared to the literature value.^{7a}

Table 2. Reactions of Imide **5a** with Cyclopentadiene and Catalysts Derived from Ligand **6d** and M(OTf)_n

metal salt ^a	endo/exo ^b	endo ee (%) ^b	yield (%) ^c	metal salt ^a	endo/exo ^b	endo ee (%) ^b	yield (%) ^c
Cu(OTf) ₂	98:2	>98	86	Mn(OTf) ₂	85:15	50	80
Ag(OTf)	nr ^d			Lu(OTf) ₃	75:25	0	75
Zn(OTf) ₂	95:5	38	85	Sm(OTf) ₃	80:20	0	78
Cd(OTf) ₂	90:10	10	80	Li(OTf)	85:15	14	89
Co(OTf) ₂	90:10	50	85	Ni(OTf) ₂	90:10	40	75

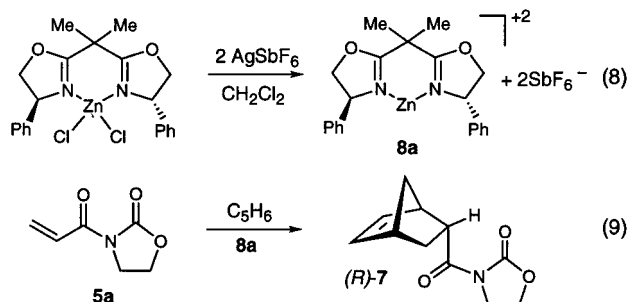
^a Reactions were run in CH₂Cl₂ with 11 mol % ligand and 10 mol % M(OTf)_n. ^b Endo/exo ratios were determined by ¹H NMR and/or chiral GLC or HPLC. Enantiomer ratios were determined either by chiral GLC or by chiral HPLC. ^c Values refer to isolated yields of cycloadducts. ^d No reaction.

In parallel with the investigation of bis(oxazoline)–Cu(OTf)₂ Lewis acid catalysts, a number of other metal triflate complexes of **6d** were evaluated (Table 2). Of the triflate salts screened, only the Cu(II)- and Zn(II)-based catalysts produced product mixtures with greater than 20:1 endo/exo diastereoselection; however, the Zn system afforded products of low endo enantioselectivity. Subsequent studies that optimized both ligand architecture and catalyst counterion for the tetrahedral Zn(II)–dienophile complex determined that the optimal Zn(II) catalyst is the phenyl-substituted complex **8a**, which affords the enantiomeric cyclopentadiene adduct (*R*)-7 in >90% yield and 92% ee (98:2 endo/exo, –78 °C, CH₂Cl₂, 8 h).^{14e,31} This observation is consistent with prior studies that have demonstrated that phenyl-substituted ligands exhibit optimal asymmetric induction in this reaction when employed with the tetrahedral Mg(II) Lewis acid (**C**, Figure 1).³² Quantitative observations on bis(oxazoline)copper and -zinc catalysts indicate that the former are more effective with respect to both conferred enantioselectivity

(31) Enantioselection (CH₂Cl₂, –78 °C) as a function of the Zn(II)–box substituent R is as follows: R = CMe₃, 56%; R = CHMe₂, 53%; R = Ph, 92%, ref 14e.

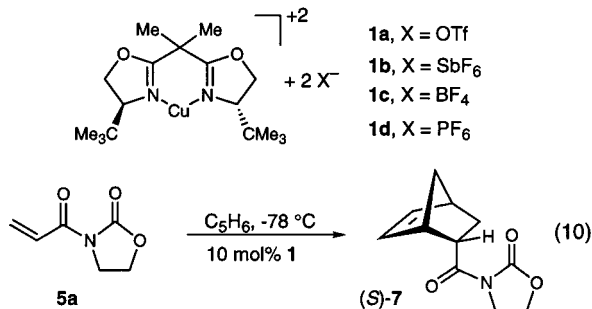
(32) See refs 13 and 14. The bias for the phenyl substituent with metals that coordinate in a tetrahedral geometry could result from both steric and electronic effects. Possible contributions from electronic effects have not yet been addressed.

tion (>98% ee vs 92% ee) and rate acceleration. The most dramatic difference between the two catalytic centers was found in their respective temperature/enantioselectivity profiles. While the Cu(II) catalysts are effective over a wide range of temperatures (vide infra), reaction enantioselectivity falls off dramatically for the Zn(II) catalysts at higher temperatures (≥ -50 °C). This point has been documented in detail elsewhere.^{14c} In a related comparative study, Engberts and co-workers have recently evaluated Cu(2+), Zn(2+), Ni(2+), and Co(2+) in metal catalyzed Diels–Alder reactions with a chelating ketone dienophile in water. In this comparison, the metal ion catalytic efficiency was found to be $\text{Co}(2+) < \text{Ni}(2+) < \text{Cu}(2+) \gg \text{Zn}(2+)$.³³



As a result of this set of experiments, the Cu(II) system emerged as the most promising candidate for further development with the bis(oxazoline) family of ligands.

Counterion Effects. In the early stages of this study, Cu(OTf)₂ was chosen as the Cu(2+) source with the assumption that the triflate counterions in the metal–ligand complex would either dissociate or be displaced readily by the chelating dienophile. On the other hand, Lewis acid catalysis through the partially dissociated ligand–metal complex, L₂CuX(1+), could well erode the performance of the fully dissociated Lewis acid L₂Cu(2+) counterpart. In addition, significant differences in Lewis acidity might be expected for the two species. Accordingly, copper(II) complexes **1b–d** were prepared by mixing CuCl₂ (or CuBr₂, 0.1 mmol), bis(oxazoline) ligand **6d** (0.11 mmol), and the appropriate silver salt AgX (0.2 mmol) in 1 mL of CH₂Cl₂.³⁴ Complexation time again proved important; vigorous stirring at room temperature for 6–8 h was required in order to provide fully active solutions. The resulting heterogeneous mixtures were filtered through Celite to give clear blue solutions of the bis(oxazoline)copper(II) complexes **1b–d**, which were used directly as catalysts (10 mol %) in the Diels–Alder reaction of acrylate imide **5a** and cyclopentadiene (eq 10).



(33) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702–7707.

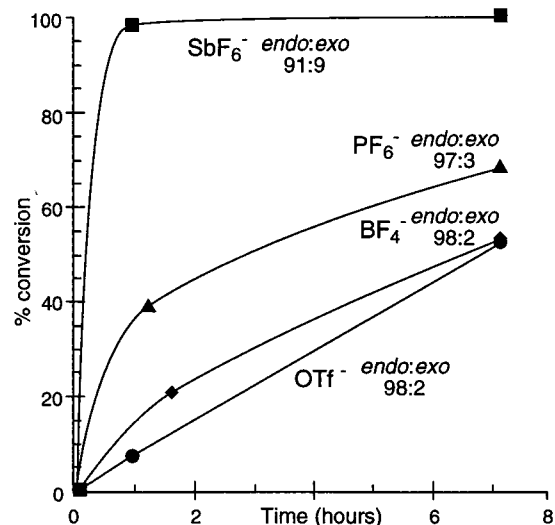


Figure 3. Conversion to (*S*)-**7** as a function of time for the reaction of acrylimide **5a** with C₅H₆ catalyzed by complexes **1a–d** at -78 °C (eq 10). The *endo* ee was >98% in all cases. *Endo/exo* ratios are provided on the graph.

The four cationic Cu(II) complexes exhibited significantly different catalytic activities in the Diels–Alder reaction (Figure 3). While the BF₄⁻ and PF₆⁻-derived catalysts **1c** and **1d** afforded rates similar to **1a** (X = OTf), [Cu((*S,S*)-*t*-Bu-box)](SbF₆)₂ (**1b**) displayed greatly enhanced catalytic efficiency. After 1 h, the percent conversion of the reaction catalyzed by **1b** was greater than that of **1a** by a factor of 20. Under the indicated reaction conditions ([**5a**] = 0.1 M, -78 °C, 10 mol % **1**),³⁵ only SbF₆⁻ complex **1b** led to complete conversion to adduct (*S*)-**7a**.³⁶ Catalyst **1b** also proved to be convenient to handle: the initial heterogeneous catalyst mixture is filtered through Celite on the benchtop. All catalysts afforded the *endo* product in >98% ee; however, the *endo/exo* ratio is dependent on the catalyst employed: the more reactive the catalyst, the less diastereoselective the Diels–Alder reaction (**1a**, *endo/exo* = 98:2; **1b**, *endo/exo* = 91:9). No explanation for this trend can be offered at this time.

Table 3. Temperature Profile of Reactions of Imide **5a** with Cyclopentadiene Catalyzed by [Cu((*S,S*)-*t*-Bu-box)](X)₂ (**1**) (Eq 10)^a

entry	catalyst	temp (°C)	time ^b	<i>endo/exo</i> ^c	<i>endo</i> ee (%) ^c
1	1a (X = OTf)	-78	10 h	98:2	>98
2	1b (X = SbF ₆)	-78	4 h	96:4	>98
3	1a (X = OTf)	25	15 min	88:12	86
4	1b (X = SbF ₆)	25	10 min	86:14	94

^a Reactions were run in CH₂Cl₂ with 10 mol % catalyst, [**5a**] = 0.3 M. ^b 100% conversion. ^c *Endo/exo* ratios were determined by ¹H NMR and/or chiral GLC or HPLC. Enantiomer ratios were determined either by chiral GLC or by chiral HPLC.

Catalyst Properties. [Cu((*S,S*)-*t*-Bu-box)](SbF₆)₂ complex **1b** was further compared to [Cu((*S,S*)-*t*-Bu-box)](OTf)₂ (**1a**). As indicated in Table 3, both catalysts function with almost complete fidelity over a range of temperatures. The reaction is

(34) Ag(I) salts have been used to generate cationic metal centers in other Diels–Alder catalysts. See ref 13b. See also: Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502–5503.

(35) The optimized conditions include a substrate concentration of 0.3 M. To allow an accurate % conversion determination, the reactions illustrated graphically in Figure 2 were [**5a**] = 0.1 M.

(36) While the study presented in Figure 3 indicates that the Diels–Alder reaction of acrylimide **5a** with cyclopentadiene is complete after 1 h at -78 °C, the reactions presented below were usually run for 4–8 h to ensure reproducibility of the results.

almost completely selective at $-78\text{ }^{\circ}\text{C}$ (entries 1 and 2, *endo* ee > 98%), and the results are still good (entry 3, *endo/exo* = 88:12, *endo* ee 86%) to excellent (entry 4, *endo/exo* = 86:14, *endo* ee 94%) at room temperature. At this temperature, the reaction is noticeably exothermic and is complete within 10–15 min. This exceptional temperature profile foreshadowed the extension of the system to less reactive dienophiles (vide infra).

[Cu((*S,S*)-*t*-Bu-box)]₂ complexes **1a** and **1b** also perform well at low catalyst loadings. Although reactions were typically screened with 10 mol % of catalyst (Table 4, entries 1 and 2), as little as 1 mol % of SbF₆ catalyst **1b** led to excellent results at $-78\text{ }^{\circ}\text{C}$ (entry 6). On the other hand, at catalyst loadings below 5 mol %, OTf complex **1a** did not promote the reaction well, even at $-50\text{ }^{\circ}\text{C}$ (entries 3 and 5).

Table 4. Effect of Catalyst Loading in Reactions of Imide **5a** with Cyclopentadiene Catalyzed by [Cu((*S,S*)-*t*-Bu-box)](X)₂ (**1**) (Eq 10)^a

catalyst	mol %	temp (°C)	time (h) ^b	<i>endo/exo</i> ^c	<i>endo</i> ee (%) ^c
1a (X = OTf)	10	-78	10	98:2	>98
1b (X = SbF ₆)	10	-78	4	96:4	>98
1a (X = OTf)	5	-50	12	97:3	96
1b (X = SbF ₆)	5	-78	4	96:4	96
1a (X = OTf)	1	-50	nr ^e		
1b (X = SbF ₆)	1	-78	8	96:4	96

^a Reactions were run in CH₂Cl₂; [**5a**] = 0.3 M. ^b 100% conversion. ^c *Endo/exo* ratios were determined by ¹H NMR and/or chiral GLC or HPLC. ^d Enantiomer ratios were determined by chiral GLC or chiral HPLC. ^e No reaction.

A study of solvent effects showed that catalysts **1a** (X = OTf) and **1b** (X = SbF₆) are tolerant of some donor solvents (Table 5). When the reaction was run in THF at $-50\text{ }^{\circ}\text{C}$ (entry 3), high selectivities and undiminished reaction rates were observed with [Cu((*S,S*)-*t*-Bu-box)](OTf)₂ (**1a**) (*endo/exo* = 97:3, *endo* ee = 98%, 4 h reaction time). This is particularly significant, as it suggests that bidentate coordination of the substrate was not compromised by the donor solvent. However, attempts to generate **1b** (X = SbF₆) in THF failed to result in the formation of soluble complex (entry 4). The use of nitromethane had little effect on the course of the reaction with either catalyst (entries 5 and 6).³⁷ This solvent tolerance is limited to non-hydroxylic oxygen-based donors, as more basic solvents impaired the reaction. For example, when acetonitrile was employed with either catalyst at $-50\text{ }^{\circ}\text{C}$ (entries 7 and 8), the rate, *endo/exo* ratio, and enantioselectivity were all diminished. Addition of 1 equiv of 2-propanol to the reaction in CH₂Cl₂ employing **1a** (X = OTf) retarded the rate and selectivities significantly (50% conversion after 4h at $-50\text{ }^{\circ}\text{C}$; *endo/exo* = 95:5, *endo* ee = 85%). In the case of **1b** (X = SbF₆), 2-propanol had little effect on the reaction rate, though the selectivity decreased markedly. In reactions of piperlyene at higher temperatures, however, 2-propanol had no effect on reaction selectivity (vide infra). Addition of 1 equiv of a tertiary amine base effectively terminated catalysis.

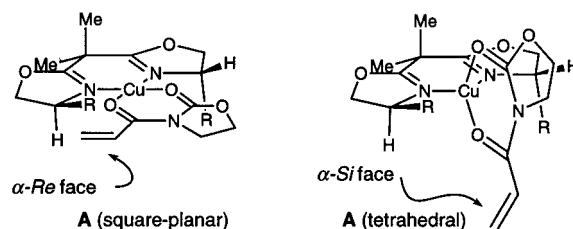
Solid-State Catalyst Characterization and Catalyst–Substrate Complex Geometry. The interpretation of the sense of asymmetric induction in the Diels–Alder reaction (eq 6) depends on an assessment of the following structural variables in the dienophile–catalyst complex: metal center geometry (square-planar vs tetrahedral), dienophile conformation (*s-cis* vs *s-trans*), and finally, the number of contacts between catalyst and dienophile (one- vs two-point binding). By analogy to our

Table 5. Solvent Effects on the Reaction of Imide **5a** with Cyclopentadiene Catalyzed by [Cu((*S,S*)-*t*-Bu-box)]X₂ (**1**) (Eq 10)^a

catalyst	solvent (temp, °C)	time (h) (conv, %)	<i>endo/exo</i> ^b	<i>endo</i> ee ^c
1a (X = OTf)	CH ₂ Cl ₂ (-50)	4 (100)	97:3	98
1b (X = SbF ₆)	CH ₂ Cl ₂ (-50)	1.5 (100)	91:9	>98
1a (X = OTf)	THF (-50)	4 (100)	97:3	98
1b (X = SbF ₆)	THF (-50)	nr ^e		
1a (X = OTf)	CH ₃ NO ₂ (-25)	4 (100)	92:8	84
1b (X = SbF ₆)	CH ₃ NO ₂ (-25)	2.5 (100)	96:4	97
1a (X = OTf)	CH ₃ CN (-50)	4 (87)	92:8	58
1b (X = SbF ₆)	CH ₃ CN (-50)	3.5 (97)	98:2	50
1a (X = OTf)	CH ₂ Cl ₂ / <i>i</i> -PrOH ^d (-50)	4 (50)	97:3	84
1b (X = SbF ₆)	CH ₂ Cl ₂ / <i>i</i> -PrOH ^d (-50)	2.5 (100)	97:3	61

^a Reactions were run with 10 mol % **1**. ^b *Endo/exo* ratios were determined by ¹H NMR and/or chiral GLC or HPLC. ^c Enantiomer ratios were determined by either chiral GLC or chiral HPLC. ^d Run with 1 equiv of *i*-PrOH (10 equiv relative to catalyst). ^e No reaction.

previous Diels–Alder studies of the chiral imides (Scheme 1),^{7b} we felt that it was reasonable to assume that two-point catalyst–dienophile binding and reaction out of the *s-cis* dienophile conformation were also occurring in these catalyzed processes. These assumptions being made, the issue of the metal coordination geometry may be addressed. As can be seen from the drawings of the dienophile–catalyst complexes (**A**), the sense of asymmetric induction is dependent on the geometry of the metal center if other structural variables are held constant. In fact, the stereochemical outcome of the catalyzed reactions is consistent with a four-coordinate square-planar Cu(II) geometry and accompanying *s-cis* dienophile geometry; these geometric constraints correlate the (*S,S*)-bis(oxazoline) ligand chirality to the observed product stereochemistry of cycloadduct (*S*)-**7**. The alternate interpretation of the observed sense of asymmetric induction would require the unlikely combination of a tetrahedral metal center and an *s-trans* dienophile conformation.



In conjunction with our efforts to understand this class of copper catalysts, we undertook an investigation of the structural basis for the remarkable reactivity and selectivity exhibited by this ligand–metal system. Attempts to characterize the solution-phase complexes by NMR experiments were unrevealing due to broadening associated with the paramagnetic d⁹ Cu center. Efforts to gain insight into solid-state structure using X-ray crystallography proved more fruitful, and three [Cu((*S,S*)-*t*-Bu-box)]X₂ X-ray crystal structures were obtained.³⁸ Despite extensive efforts to obtain ternary complexes of **1a** and **1b** incorporating dienophile **5a**, the highly crystalline bis(aquo) complexes **9a** and **9b** were repeatedly obtained, even under the nominally anhydrous conditions afforded by a drybox. Preparatively, [Cu((*S,S*)-*t*-Bu-box)(H₂O)₂](OTf)₂ (**9a**) was produced by exposure of a green CH₂Cl₂ solution of **1a** to the atmosphere; blue crystals of the hydrated complex gradually formed at room temperature. The analogous bis(aquo) SbF₆ complex **9b** was

(37) Jørgensen has recently reported the use of nitromethane in [Cu(box)]X₂-catalyzed hetero Diels–Alder and ene reactions. Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, 52, 7321–7328.

(38) The structures of **9a** and **9b** have been reported. **9a**: (a) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 3372–3375. **9b**: (b) Reference 27c.

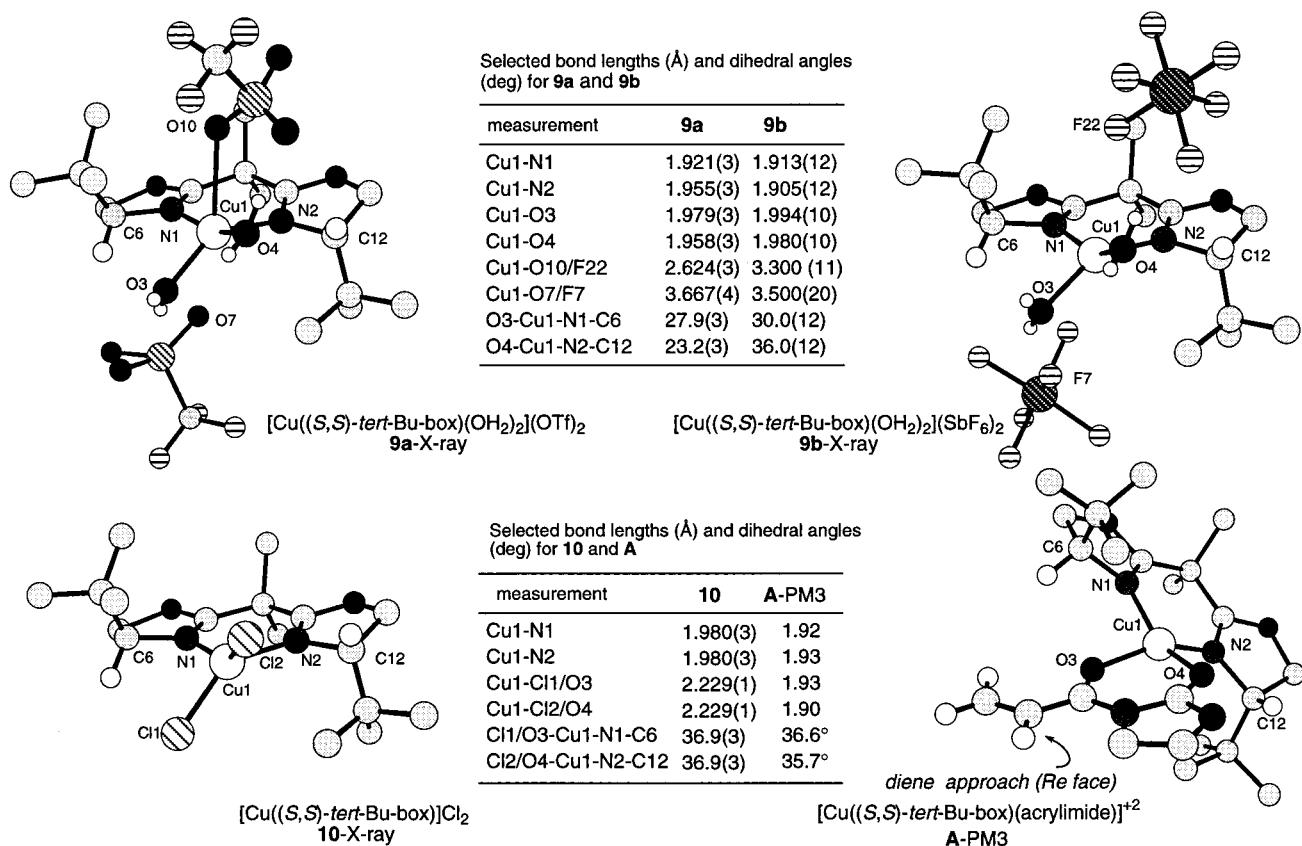
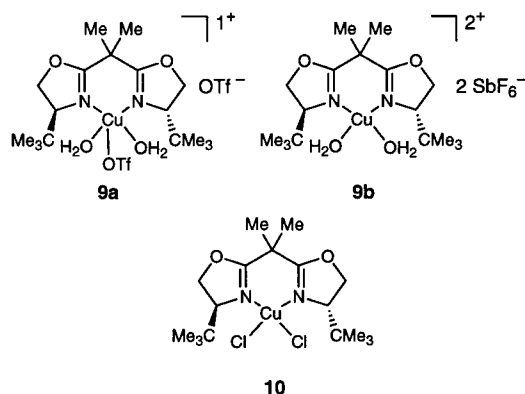


Figure 4. Crystallographic structures of bis(aquo) complexes **9a**-X-ray and **9b**-X-ray, and dichloride complex **10**-X-ray, and calculated structure of **A-PM3**, along with selected bond lengths and dihedral angles.

similarly produced by exposure of **1b** to atmospheric moisture. Diffractable crystals of $[\text{Cu}((S,S)\text{-}t\text{-Bu-box})\text{Cl}_2]$ (**10**) were prepared by slow evaporation of a CH_2Cl_2 solution.



The X-ray structures of these complexes are illustrated in Figure 4 along with selected bond lengths and angles. Notable features of these structures include monomeric, bidentate coordination of the bis(oxazoline) ligand to the Cu center and coordination spheres in which the bis(oxazoline) and water (or chloride) ligands are arrayed in geometries intermediate between planar and tetrahedral. This former feature is in marked contrast to the helical, polymeric bis(oxazoline)-Cu(I) complex which has been prepared in this laboratory.³⁹

The crystallographic data for triflate complex **9a** reveal a distorted square-pyramidal geometry, with one triflate counterion weakly bound to the metal center in the apical position (Cu-OTf = 2.624 Å), while the other is fully dissociated (Cu-OTf

= 3.667 Å). The average degree of distortion of the coordinated water molecules from the copper-ligand plane is 26°. The crystallographic data for SbF_6 complex **9b** (Figure 4) demonstrate that neither counterion is coordinated to the Cu center, which is disposed in a distorted square-planar geometry, with an average degree of distortion of the coordinated water molecules from the copper-ligand plane of 33°. The structure of C_2 -symmetric dichloride complex **10** likewise displays a distorted (37°) square-planar geometry.

The rate-retarding effect of the triflate-based catalyst **1a** can be explained by invoking triflate association with the catalyst substrate-complex, as suggested by structure **9a**. IR spectroscopy affords the opportunity of determining whether triflate counterions are dissociated in solution through observation of the characteristic vibrational frequencies which are attributed to bound and unbound triflate ions.⁴¹ Frequencies at both 1380 (bound $-\text{OSO}_2\text{CF}_3$) and 1280 cm^{-1} (unbound $-\text{OSO}_2\text{CF}_3$) were observed, presumably due to the presence of multiple species.

In speculating on how imide dienophiles associate with **1a** and **1b**, one might replace the bound equatorial ligands in the X-ray structures with the imide carbonyl oxygens. Inspection of molecular models reveals that, when the imide dienophile is superimposed onto the positions occupied by the H_2O (or Cl) ligands in the X-ray structures, diene trajectory analysis leads to the prediction of the correct cycloadduct enantiomer. It is apparent that small distortions from square-planarity do not result in exposure of the opposite olefin diastereoface until the distortion more closely resembles the tetrahedral geometry.

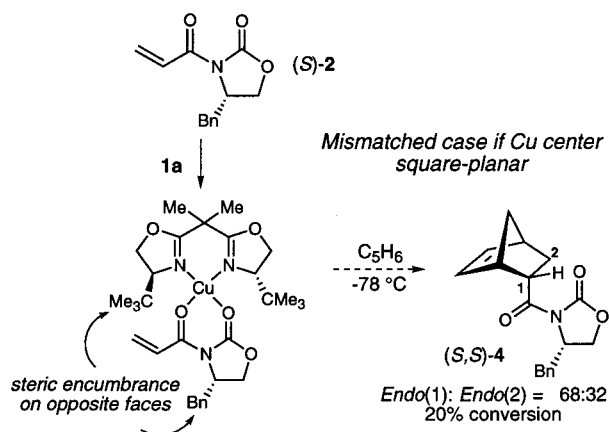
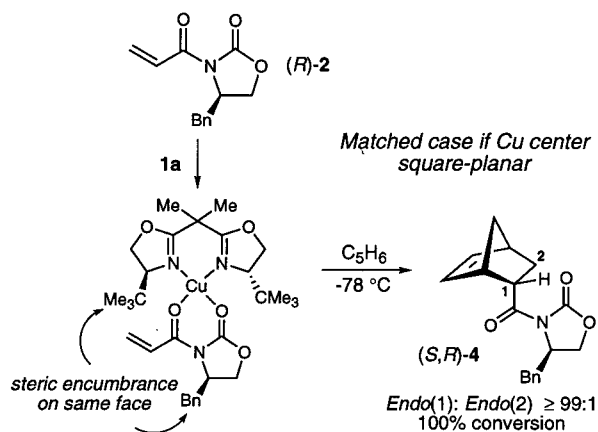
Calculations were performed to provide representations of the catalyst-substrate complex. Calculated $[\text{Cu}((S,S)\text{-}t\text{-Bu-box})-$

(39) Evans, D. A.; Woerpel, K. A.; Scott, M. S. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430-432.

(40) Four-coordinate Cu(II) complexes exhibit a strong tendency toward square-planar geometries. See ref 28.

(41) Lawrence, G. A. *Chem. Rev.* **1986**, *86*, 17-33.

Scheme 2



(acrylimide)](2+) complex **A-PM3** is illustrated in Figure 3. It is noteworthy that the degree of distortion from square-planarity was approximately that found in the X-ray structure of bis(aquo) complex **9b**. Furthermore, the complex clearly predicts the stereochemical outcome of the Diels–Alder reactions.^{7a,c} These structural data complement solution-phase EPR data, which are consistent with square-planar catalyst–acrylimide complexes.⁴² In summary, we believe that the X-ray and computed structural data support a catalyst–substrate geometry which is, indeed, square-planar, but which is distorted from the idealized dihedral angles to some extent.

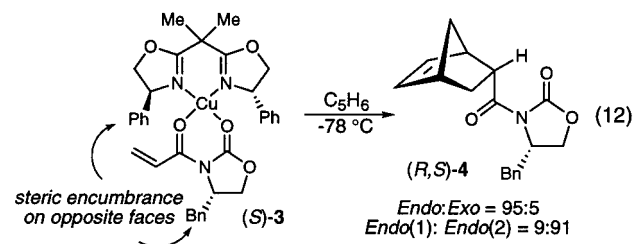
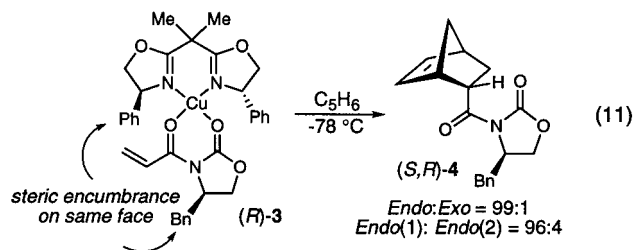
The preceding analysis indicates that the corresponding chiral tetrahedral metal–bis(oxazoline) complexes should exhibit the opposite sense of asymmetric induction. In this regard, it is noteworthy that Zn(II) catalyst **8a** and Corey's Mg(II)-derived catalyst **C** (Figure 1), which are believed to proceed through tetrahedral catalyst–substrate complexes, produce the (*R*)-7 cycloadduct as the major product, in accord with expectation.

Double-Stereodifferentiating Experiments. In the absence of X-ray structural confirmation of the proposed catalyst–imide complex, we investigated double-stereodifferentiating experiments with the chiral imides (*R*)-2 and (*S*)-2 and chiral triflate catalyst **1a**. These experiments were designed to determine whether the principal assumptions of two-point catalyst–dienophile binding, metal center geometry, and dienophile conformation that were made in both the auxiliary-based reaction and the chiral-catalyzed counterpart behaved in an internally consistent fashion. The stereochemically matched and mismatched reactions are illustrated in Scheme 2. If the catalyst–substrate complex maintains a square-planar coordination geometry during the catalyzed process, then the reaction of (*R*)-2 should represent the stereochemically matched case, where the chiral elements from both ligand and substrate cooperate to block the *Si* face of the dienophile. In contrast, use of the enantiomeric dienophile (*S*)-2 should present a situation where one face of the dienophile is blocked by the substrate substituent, and the other by the ligand substituent, creating a mismatched case. The intermediacy of a tetrahedral coordination environment for the catalyst–substrate complex would predict the opposite results.

Results fully consistent with the square-planar model involving the *s-cis* chelated dienophile were obtained. Under identical reaction conditions (CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 11 h, 10% **1a** (X = OTf), dramatically different results were observed using the enantiomeric dienophiles (*R*)- and (*S*)-2. In the matched case employing (*R*)-2, the reaction proceeded to completion with essentially perfect stereocontrol ($\text{endo/exo} > 99:1$, $\text{endo}(1)/\text{endo}(2) = 99:$

1) to afford the adduct (*S,R*)-4 in 87% isolated yield. In contrast, with (*S*)-2, the reaction proceeded to only 20% conversion during the 11-h period with very low diastereoselectivity ($\text{endo/exo} = 97:3$, $\text{endo}(1)/\text{endo}(2) = 68:32$). It is noteworthy that, in the mismatched case, the principle *endo* adduct (*S,S*)-4 corresponds to that derived from the catalyst-controlled, rather than the substrate-controlled process, a testament to the stereochemical dominance of the **6d**–Cu(OTf)₂ catalyst and to the torsional stability of the square-planar copper center.

The preceding experiments suggest that the Diels–Alder reactions of (*R*)- and (*S*)-2 should revert to conventional substrate-based stereoselection as the stereochemical bias imparted by the copper catalyst is attenuated. This projected trend was evaluated with the poorly enantioselective phenyl-substituted complex **6a**–Cu(OTf)₂ (Table 1), and the results were in accord with prediction (eqs 11 and 12). As expected, the stereochemically matched catalyst and dienophile (*R*)-2 (eq 11) (CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 11 h, 10 mol % **6a**–Cu(OTf)₂) afforded the expected cycloadduct (*S,R*)-4 with high diastereoselectivity (100% conversion, $\text{endo/exo} = 99:1$, $\text{endo}(1)/\text{endo}(2) = 96:4$). In the mismatched alternative, using dienophile (*S*)-2 (eq 12), the reaction likewise proceeded to completion ($-78\text{ }^\circ\text{C}$, 11 h), affording (*R,S*)-4 as the major product ($\text{endo/exo} = 95:5$, $\text{endo}(1)/\text{endo}(2) = 9:91$). This stereochemical outcome indicates that the bias imparted by the dienophile now dominates the process, and while the **6a**–Cu(OTf)₂ complex is providing the necessary chelate organization and Lewis acid activation for the cycloaddition, its stereochemical influence is minimal.



(42) Kozlowski, M. C., unpublished results.

Anhydrous vs Aquo Complexes.⁴³ The isolation of crystalline aquo complexes [Cu((*S,S*)-*t*-Bu-box)(H₂O)₂](OTf)₂ (**9a**) and [Cu((*S,S*)-*t*-Bu-box)(H₂O)₂](SbF₆)₂ (**9b**) presented the possibility that they could be employed as bench-stable Diels–Alder catalysts. Therefore, these complexes were compared with their anhydrous counterparts **1a** (X = OTf) and **1b** (X = SbF₆) in their ability to catalyze Diels–Alder reactions. Since it has been demonstrated that the reaction of imide **5a** with piperylene is catalyzed by either **1a** or **1b** with excellent selectivities at ambient temperature,⁶ this reaction was employed to determine the relative reactivities of the various complexes (eq 13, Table 6).

Triflate complex **1a** (10 mol %) promoted the reaction to 94% conversion in 15 h. Cis cycloadduct **11** was formed in 84% ee, and the major enantiomer accounted for 73% of the reaction product mixture (entry 1). When bis(aquo) complex **9a** (X = OTf) was employed under equivalent conditions, less than 10% conversion took place in 24 h, attesting to the detrimental effect of hydration on this catalyst (entry 2). Molecular sieves proved efficacious in reactivating the catalyst, however. When complex **9a** was stirred first with 3-Å sieves for 2.5 h, and then employed in the reaction, 95% conversion was obtained after 15 h (entry 3). The product was formed with the same selectivity as in the reaction employing the anhydrous catalyst.

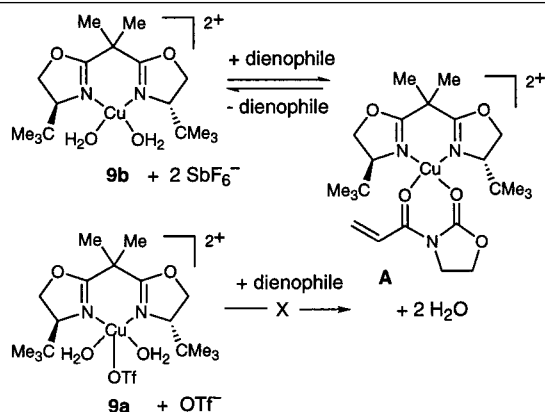
The response of [Cu((*S,S*)-*t*-Bu-box)](SbF₆)₂ (**1b**) to hydration was surprisingly different. The anhydrous catalyst required only 50 min to promote the reaction to complete conversion; the major isomer was formed in 95% ee and accounted for 82% of the reaction mixture (entry 4). Bis(aquo) complex **9b** was almost as active: the reaction proceeded to completion in only 70 min, with equivalent selectivities (entry 5). However, while sieves fully regenerated the triflate catalyst, they suppressed the activity of SbF₆⁻ catalyst **9b**, and only 10% conversion was observed after 4 h. The fact that hydration does not have a large effect on [Cu((*S,S*)-*t*-Bu-box)](SbF₆)₂ (**1b**) suggested that this catalyst should tolerate hydroxylic additives. As described above, the addition of 1 equiv of 2-propanol (10 equiv relative to catalyst) to reactions of acrylimide **5a** with cyclopentadiene dramatically lowered both rates and selectivities at -50 °C (Table 5). When 2-propanol was similarly added to the reaction of piperylene catalyzed by **1b** (X = SbF₆) at room temperature, the reaction rate was halved, but the selectivity was unchanged. We postulate that, at -50 °C, 2-propanol remains associated with the catalyst throughout the reaction.

Based on the preceding observations, we postulate that an open fifth coordination site on the Cu(2+) center is required for catalyst turnover through the associative displacement of the bound neutral oxygen ligands (water or Diels–Alder adduct) by additional dienophile (Table 2). The X-ray structures of the hydrated copper–ligand complexes **9a** and **9b** (Figure 4) illustrate that one of the triflate counterions in **9a** remains bound to the metal center in the solid state. Evidence accumulated to date implicates triflate ion association throughout the catalytic cycle. These subtle observations on the influence of counterion structure on catalyst turnover were critical to our development of the glyoxylate ene reaction, which was initially observed as a stoichiometric process with [Cu((*S,S*)-*t*-Bu-box)](OTf)₂ (**1a**) and later rendered catalytic with [Cu((*S,S*)-*t*-Bu-box)](SbF₆)₂ (**1b**) and its hydrated counterpart **9b**.⁴⁴

(43) Engberts has recently reported water-enhanced enantioselectivity in a Diels–Alder reaction: Otto, S.; Boccaletti, G.; Engberts, J. *J. Am. Chem. Soc.* **1998**, *120*, 4238–4239. For other uses of aquo complexes in Diels–Alder reactions, see refs 21, 24c, and 38a.

Table 6. Diels–Alder Reactions of Imide **5a** with Piperylene Catalyzed by [Cu(*t*-Bu-box)(H₂O)_{*n*}](X)₂ Complexes (Eq 13)^a

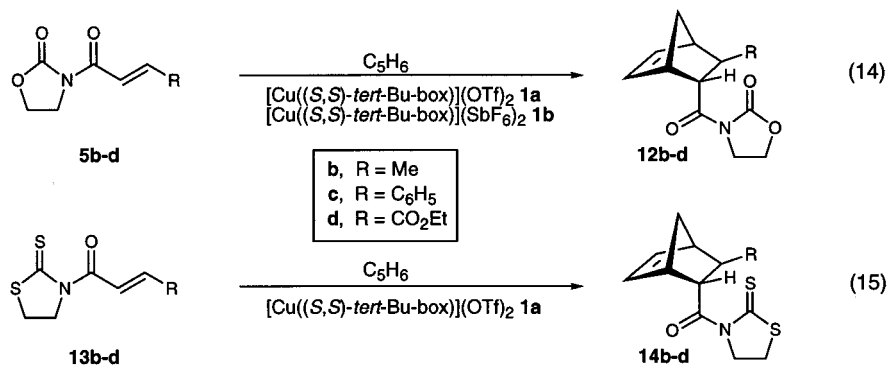
catalyst	sieves	time	conv (%) ^b	selectivity ^{c,d}	ee, 11 (%) ^d
1a (X = OTf)	no	15 h	94	73:27	84
9a (X = OTf)	no	24 h	<10	nd	nd
9a (X = OTf)	yes	15 h	95	74:26	85
1b (X = SbF ₆)	no	50 min	100	82:18	95
9b (X = SbF ₆)	no	70 min	100	83:17	94
9b (X = SbF ₆)	yes	4 h	10	nd	nd



^a Reactions were run in CH₂Cl₂, with 10 mol % catalyst and 10 equiv of piperylene. In reactions with sieves, the catalyst was stirred with 3-Å molecular sieves for 150 min before reaction. ^b Conversion was determined by NMR analysis of unpurified reaction mixture. ^c Ratio refers to major cis:Σ(other isomers). ^d Selectivity and major enantioselectivity were determined by chiral GC analysis of the unpurified reaction mixture. nd = not determined.

β-Substituted Dienophiles. We next sought to examine the generality of the reaction with cyclopentadiene in the context of modifying the dienophile structure. When β-substituted dienophiles were employed in the cycloaddition reaction, good reactivities and selectivities were observed throughout the range of imides surveyed (eq 14, Table 7). While [Cu((*S,S*)-*t*-Bu-box)](OTf)₂ (**1a**) provided highly enantioselective reactions, it was in the investigation of these substrates that the potential of the SbF₆⁻-derived catalyst **1b** became fully apparent. For example, with **1a** (X = OTf) as catalyst, crotonate derivative **5b** underwent a highly enantioselective reaction with cyclopentadiene at -15 °C (30 h), affording cycloadduct **12b** in 85% yield after 30 h (entry 2, *endo/exo* = 96:4, *endo* ee = 97%). Using **1b** (X = SbF₆), the cycloadduct was isolated in 99% yield and a remarkable 99% ee after only 20 h at -15 °C (entry 4, *endo/exo* = 85:15); these numbers are taken from a large-scale reaction employing 150 mmol (23 g) of crotonate imide **5b**. At room temperature, both catalysts afforded high yields of **12b** after 8 h, with only slightly diminished enantioselectivities (entries 1 and 3, *endo* ee = 94 and 96%, respectively). In the case of cinnamate derivative **5c** reaction at 25 °C was required with **1a** (X = OTf) for a reasonable rate of conversion, but good selectivity was retained and product **12c** was isolated in 85% yield after 24 h (entry 6, *endo/exo* = 90:10, *endo* ee = 90%). Under the same conditions (25 °C, 24 h) with catalyst **1b** (X = SbF₆), **12c** was isolated in improved yield (96%) and

(44) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojtkovsky, T.; Tregay, S. T. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825.

Table 7. Enantioselective Diels–Alder Reactions of β -Substituted Dienophiles **5** and **13** with Cyclopentadiene Catalyzed by **1a** (X = OTf) and **1b** (X = SbF₆) (Eqs 14 and 15)^a

entry	dienophile	catalyst	time (h) (temp, °C)	<i>endo/exo</i> ^b	<i>endo ee</i> (%) ^c	yield (%) ^d	product
1	5b (R = Me)	1a (X = OTf)	8 (25)	87:13	94	95	12b (R = Me)
2	5b (R = Me)	1a (X = OTf)	30 (−15)	96:4	97	85	12b (R = Me)
3	5b (R = Me)	1b (X = SbF ₆)	8 (25)	82:18	96	98	12b (R = Me)
4	5b (R = Me)	1b (X = SbF ₆)	20 (−15)	85:15	99	99	12b (R = Me)
5	13b (R = Me)	1a (X = OTf)	36 (−45)	96:4	94 ^e	82	14b (R = Me)
6	5c (R = Ph)	1a (X = OTf)	24 (25)	90:10	90 ^f	85	12c (R = Ph)
7	5c (R = Ph)	1a (X = OTf)	48 (−10)	93:7	94 ^f	16	12c (R = Ph)
8	5c (R = Ph)	1b (X = SbF ₆)	24 (25)	81:19	96 ^f	96	12c (R = Ph)
9	5c (R = Ph)	1b (X = SbF ₆)	48 (−10)	88:12	98 ^f	77	12c (R = Ph)
10	13c (R = Ph)	1a (X = OTf)	72 (−35)	92:8	97 ^f	86	14c (R = Ph)
11	5d (R = CO ₂ Et)	1a (X = OTf) ^g	20 (−55)	94:6	95 ^h	92	12d (R = CO ₂ Et)
12	5d (R = CO ₂ Et)	1b (X = SbF ₆)	20 (−55)	82:18	87 ^h	88	12d (R = CO ₂ Et)
13	13d (R = CO ₂ Et)	1a (X = OTf) ^g	20 (−55)	84:16	96 ^h	88	14d (R = CO ₂ Et)

^a Reactions were run at the indicated temperature in CH₂Cl₂ with 10 mol % catalyst, unless otherwise noted. ^b Diastereomer ratios were determined by ¹H NMR. ^c Enantiomer ratios were determined by chiral HPLC or chiral GLC. ^d Values refer to isolated yields of cycloadducts. ^e Enantiomer ratio was determined by conversion to **12b**. ^f Enantiomer ratio was determined by conversion to the corresponding α -methyl benzyl amide. ^g Reactions were performed in the presence of 5 mol % **1a** (X = OTf). ^h Enantiomer ratio was determined by conversion to the corresponding iodolactone.

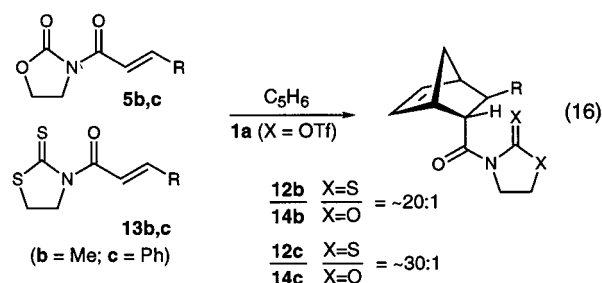
enantiomeric purity (96% ee, entry 8). Lowering the reaction temperature to −10 °C when employing catalyst **1b** (X = SbF₆) provided the product in 98% ee and 77% isolated yield (48 h, entry 9). Catalyst **1a** led to an impractically slow reaction at this temperature, albeit with high selectivity (94% ee, entry 7). The fumarate derivative **5d** was very reactive and was transformed to **12d** in 92% isolated yield at low temperature (−55 °C), employing only 5 mol % catalyst **1a** (X = OTf) (entry 11). Selectivities were high with this substrate (*endo/exo* = 94:6, *endo ee* = 95%), despite the possibility that Lewis acid activation at the ester terminus threatened to erode the selectivity for this substrate. This alternative binding mode may happen, though, in the case of catalyst **1b** (X = SbF₆), which afforded the cycloadduct in 88% yield (*endo/exo* = 82:18), with a diminished enantioselectivity of 87% ee (entry 12).

To increase the reactivity of the β -substituted dienophiles, we investigated the use of α,β -unsaturated thiazolidine-2-thione derivatives **13b–d** (eq 15, Table 7).⁴⁵ Though there was some concern that sulfur-based dienophiles would bind irreversibly to the copper(II) center, poisoning of catalyst **1a** (X = OTf) was not observed. The Diels–Alder reaction of crotonate-derived **13b** (entry 5) proceeded to completion within 36 h at −45 °C, and product **14b** was formed with selectivity comparable to oxygen analogue **12b** (*endo/exo* = 96:4, *endo ee* = 94%). In the case of cinnamate-derived **13b**, the greater substrate reactivity permitted lower reaction temperatures, resulting in enhanced selectivities (entry 10). Complete reaction was observed after 72 h at −35 °C, and the cycloadduct was obtained in 86% isolated yield (*endo/exo* = 92:8, *endo ee* = 97%). Again,

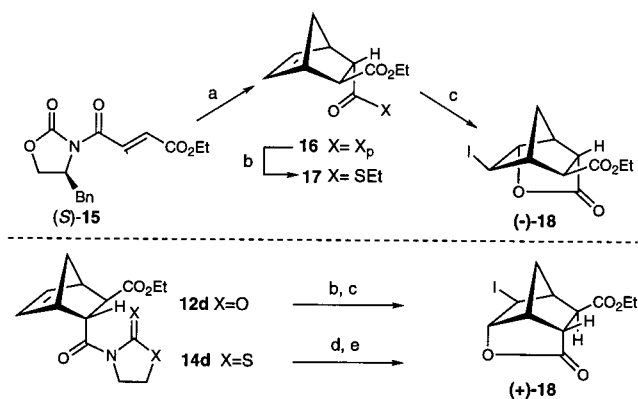
fumarate dienophile **13d** was exceptionally reactive; the reaction proceeded efficiently with 5 mol % catalyst at −55 °C, and cycloadduct **14d** was obtained in 88% yield as a 84:16 mixture of *endo/exo* isomers (entry 13, *endo ee* = 96%).

While poisoning was not observed in reactions employing complex **1a** (X = OTf), catalyst **1b** (X = SbF₆) was inactivated upon addition of the sulfur-containing substrates, which were recovered in moderate yields (60–70%). A control reaction of **13b** (R = Me) with cyclopentadiene in the presence of stoichiometric quantities of copper(II) complex **1b** (X = SbF₆) afforded adduct **14b** in 78% yield and 94% ee (10 h, 0 °C), highlighting turnover as the problematic step in this reaction.

Using [Cu((*S,S*)-*t*-Bu-box)](OTf)₂ (**1a**), a direct competition experiment between crotonate derivatives **5b** and **13b** showed the latter to be 20 times more reactive; similarly, **5c** (R = Ph) was found to be roughly 30 times more reactive than **13c** (eq 16). While these observations may reflect a greater affinity of thiazolidine-2-thione derivatives for the catalyst relative to their oxygen counterparts more than any inherent increase in dienophilicity, the end result is that, for catalyst **1a** (X = OTf), β -substituted sulfur-based dienophiles uniformly afford enhanced reactivity in the catalyzed Diels–Alder reaction.



(45) These heterocycles exhibit higher reactivity in acyl-transfer reactions. See, for example: Hsiao, C. N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206.

Scheme 3^a

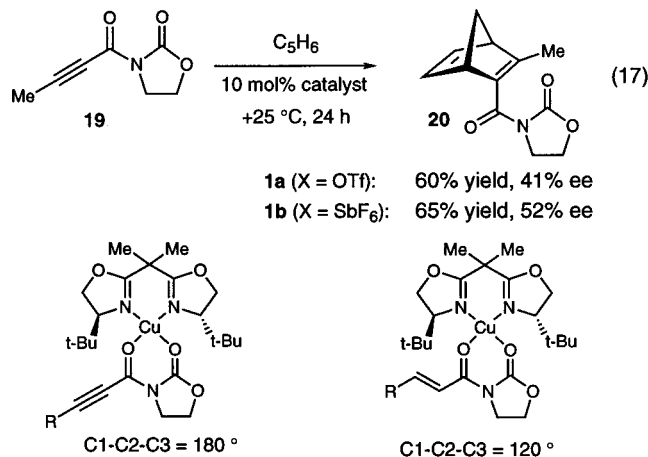
^a Conditions: (a) 1.4 equiv of Et₂AlCl, CpH, CH₂Cl₂, -78 °C; (b) LiSEt, THF, 0 °C; (c) Hg(O₂CCF₃)₂, THF/H₂O, I₂; (d) LiOH, THF/H₂O; (e) I₂, CH₃CN.

The absolute stereochemical assignments of cycloadducts **12b,c** and **14b,c** were secured by conversion to the benzyl esters, which were compared to material derived from Me₂AlCl-promoted cycloaddition reactions employing chiral *N*-acyl imide dienophiles.⁷ The absolute stereochemical assignments of cycloadducts **12d** and **14d** were also made by correlation to the product of an auxiliary-based Diels–Alder reaction (Scheme 3). Treatment of (*S*)-**15** with Et₂AlCl (1.4 equiv, -78 °C) followed by cyclopentadiene (30 min, -78 °C) afforded an 87:13 mixture of *endo/exo* cycloadducts (*endo*(1)/*endo*(2)) = 95:5). The absolute stereochemistry of the major *endo* cycloadduct **16** was assigned by analogy to our earlier studies.⁷ Cleavage of the oxazolidinone auxiliary was accomplished by treatment of **16** with LiSEt according to the method of Damon.⁴⁶ Conversion of thioester **17** to iodolactone (–)-**18** was then achieved by treatment with aqueous Hg(O₂CCF₃)₂, followed by trapping of the intermediate organomercurial species with I₂. The absolute stereochemical assignment (–)-**18** was confirmed by converting the product to the known (5*S*,6*S*)-bis(hydroxymethyl)bicyclo-[2.2.1]hept-2-ene and comparing the optical rotation (90% ee by chiral GLC, [α]_D –18° (c 0.14, CHCl₃); lit. [α]_D –23° (c 0.80, CHCl₃).⁴⁷

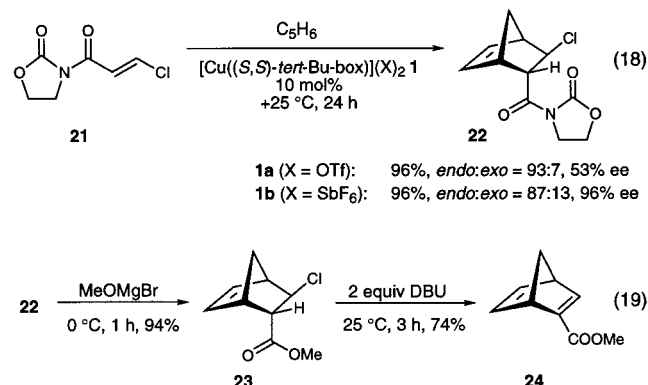
Diels–Alder adducts **12d** and **14d** were also converted to the iodolactones. Cycloadduct **12d** underwent a procedure analogous to that used for adduct **16**. Cycloadduct **14d** was converted to the corresponding acid, and subsequent iodolactonization then afforded the desired product. As anticipated, the products obtained in reactions catalyzed by copper(II) catalysts **1a** (X = OTf) and **1b** (X = SbF₆) afforded (+)-**18**, confirming that the Cu(II)-catalyzed cycloaddition reaction is stereoregular throughout the range of β-substituted dienophiles examined.

Acetylenes and Acetylene Equivalent Dienophiles. An effective acetylenic dienophile in the asymmetric Diels–Alder reaction would represent a highly desirable and novel approach to chiral, pharmacologically active synthetic intermediates.⁴⁸ Butynoate-derived imide **19** was prepared and studied in the catalyzed cycloaddition with cyclopentadiene (eq 17). The reactivity of **19** was low; catalyst **1a** (X = OTf) promoted the

reaction to only 60% conversion after a 24-h period at 25 °C, affording product **20** in 41% ee. SbF₆-derived **1b** likewise afforded the product in 52% ee and in 65% yield. These results are congruent with earlier studies from our laboratory involving alkynes in auxiliary-based reactions.^{7a} Acetylenes present a special challenge for the Diels–Alder process since they possess two orthogonal sets of π-orbitals, each of which can, in principle, participate in a cycloaddition reaction.⁴⁹ In addition, the C1–C2–C3 bond angle of 180° of the β-substituted propiolate creates an environment wherein the π-system undergoing cycloaddition is projected away from the chirality associated with the Lewis acid catalyst. In contrast, the 120° C1–C2–C3 bond angle of β-substituted acrylates projects the reacting double bond back toward the chiral substituent.



An alternative tactic would be to employ a β-substituted imide incorporating a group that could be eliminated after the cycloaddition. β-Chloroacrylimide **21** was viewed as a possible acetylene equivalent that would hold the reacting centers in proximity to the ligand chirality (eq 18).⁵⁰ With catalyst **1a** (X = OTf), cycloadduct **22** was obtained with modest selectivity (*endo/exo* = 93:7, *endo* ee = 53%). Gratifyingly, the use of SbF₆-derived catalyst **1b** afforded **22** after 18 h at room temperature in 96% yield, with an excellent *endo* enantioselectivity of 95% (*endo/exo* = 87:13, *exo* ee 85%). These numbers were taken from an experiment run on 62 mmol (11 g) of **21**. Recrystallization yielded enantiomerically pure **22**. Transesterification to methyl ester (**23**, MeOMgBr, 0 °C, 1 h), followed by elimination (2 equiv DBU, room temperature, 3 h), cleanly afforded 2-(methoxycarbonyl)norbornadiene (**24**) (eq 19).



(46) (a) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849–2852. (b) See also ref 8.

(47) (–)-**18** was subjected to a two-step sequence [(a) *t*-BuLi, (b) LAH] to afford the diol, which has been reported: Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135–161.

(48) For example, chiral norbornadienes would be useful starting materials for the synthesis of prostaglandins. Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelson, B. *Tetrahedron Lett.* **1976**, *17*, 737–740.

(49) For successful approaches to this problem, see: (a) Ishihara, K.; Kondo, S.; Kurihara, H.; Yamamoto, H.; Ohashi, S.; Inagaki, S. *J. Org. Chem.* **1997**, *62*, 3026–3027. (b) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755–5758.

(50) Norris, W. P. *J. Org. Chem.* **1968**, *33*, 4540–4541.

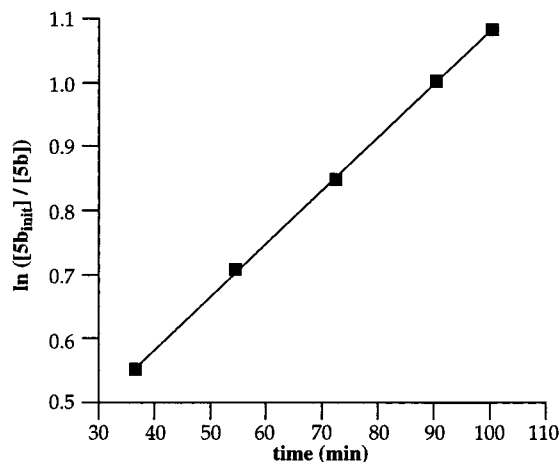
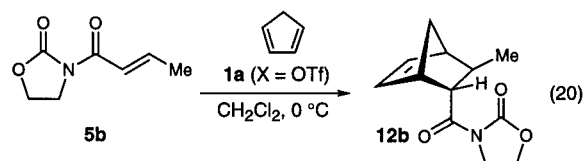


Figure 5. Pseudo-first-order kinetics for the early stages of reaction of **5b** with C_5H_6 and catalyst **1a** ($X = OTf$) (eq 20).

Reaction Kinetics. The possibility of product inhibition affecting the catalysis of the Diels–Alder reaction, while often implied in various catalytic processes, has rarely been quantified.⁵¹ Fortunately, through some relatively straightforward experiments, the role of product inhibition can be clearly diagnosed.⁵² Kinetics experiments were performed at 0 °C on the Diels–Alder reaction of the well-behaved crotonate imide **5b**, where cyclopentadiene (10 M) was present in large excess relative the concentration of dienophile (0.49 M), which was, in turn, large relative to the concentration of catalyst **1a** ($X = OTf$, 0.049 M, eq 20).⁵³ The background reaction was determined to be negligible at 0 °C, and cyclopentadiene dimerization was slow relative to the overall rate of the reaction.⁵⁴ Aliquots were taken at specified time intervals and quickly quenched in a rapidly stirred ice-cold mixture of ethyl acetate/saturated $NaHCO_3$, and the residual cyclopentadiene was removed under vacuum at 0 °C. Products were quantified by GC analysis with 4,4'-di-*tert*-butyldiphenyl as the internal standard.



Under these conditions, the reaction was found to follow first-order kinetics at low substrate conversions (rate = $k'[\mathbf{5b}]$), as indicated by the linear plot of $\ln\{[\mathbf{5b}]_{init}/[\mathbf{5b}]_{init} - [\mathbf{5b}]\}$ versus time (Figure 5), the slope of which equals the phenomenological rate constant k' , which, under the specified conditions, was found to be $8.3 \times 10^{-3} M^{-2} min^{-1}$. As substrate conversion increased (to greater than 30%), downward curvature became noticeable in the plot (Figure 6), which no longer could be well-fitted to a linear equation. This fact would seem to indicate that product inhibition and/or catalyst decomposition was playing a role. Consequently, we chose to perform subsequent kinetics runs in the region of first-order behavior, where catalyst concentration is assumed to be constant.

(51) Kobayashi has recently reported an interesting lanthanide-based Diels–Alder catalyst which turns over the sense of induction in the presence of potentially two-point binding competitive inhibitors: see ref 18b.

(52) A discussion on inhibition by Laidler was found to be informative. Laidler, K. J. *Chemical Kinetics*; Harper and Row: New York, 1987.

(53) A kinetic analysis has been done of a similar system: Chow, H.-F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116–5127.

(54) At the concentration of cyclopentadiene employed in the standard kinetics run at 0 °C, dimerization was ascertained to be a maximum of 4% over a 24 h period.

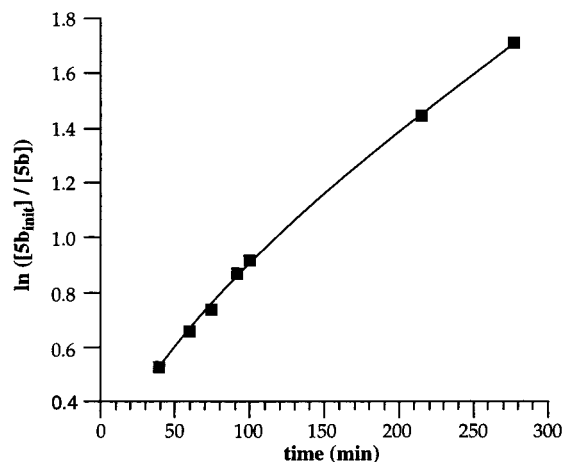
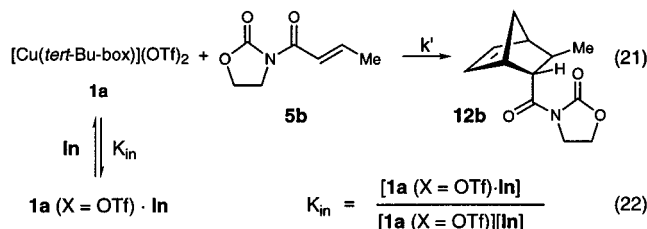


Figure 6. Downward curvature in the log plot of the reaction of **5b** with C_5H_6 and catalyst **1a** ($X = OTf$) (eq 20).

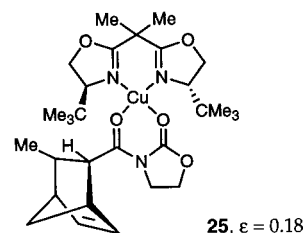
When a competitive inhibitor (In) is present, the kinetic scheme shown in eq 21 applies, where K_{in} represents the equilibrium constant for dissociation of the inhibitor–catalyst complex (eq 22):



The competitive inhibitor can be the product of the reaction itself. For instance, when a kinetics run was performed in the presence of added adduct **12b** at 0 °C ($[\mathbf{12b}] = 0.98 M$ at $t = 0$), an 18% reduction in rate was observed. Once again, the reaction followed pseudo-first-order kinetics at low conversions of substrate. For a given concentration of inhibitor, we can quantify the degree of inhibition as

$$\epsilon = \frac{\nu_0 - \nu}{\nu_0} \quad (23)$$

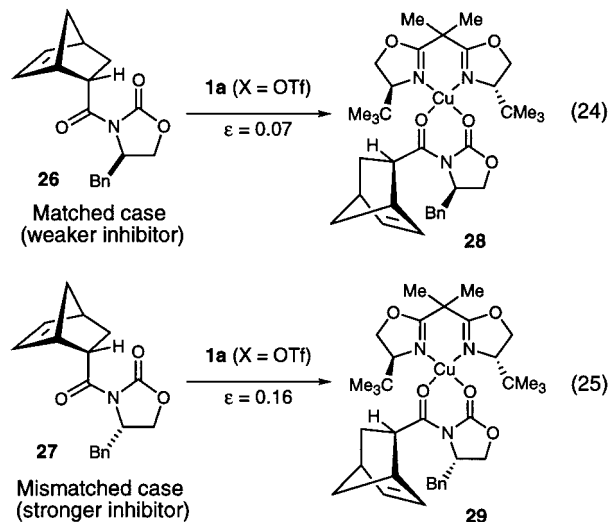
where ν_0 is the rate of reaction in the absence of inhibitor, and ν is the rate in the presence of inhibitor, so that an 18% reduction in rate gives $\epsilon = 0.18$. Additionally a value for K_{in} of $0.23 M^{-1}$ can be estimated if we assume that the 18% reduction in rate is attributable to an 18% effective reduction in the concentration of catalyst through formation of a nonproductive catalyst–inhibitor complex, such as **25**.⁵⁵



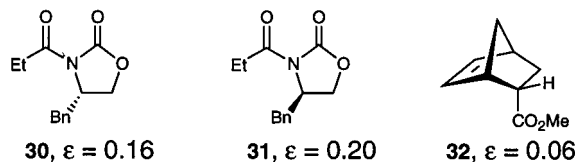
(55) If the concentration of catalyst = x , and the degree of inhibition = ϵ , then the following equation relates K_{in} to x and ϵ :

$$K_{in} = \frac{[x\epsilon]}{[x - x\epsilon][In - x\epsilon]}$$

Even more interesting is the observation of double-stereo-differentiating competitive inhibition in the reaction of **5b** with cyclopentadiene in the presence of the diastereomerically pure adducts **26** and **27**. Runs were performed at concentrations of catalyst **1a** ($X = \text{OTf}$) (10 mol % in metal, 11 mol % ligand), substrate (0.49 M), and inhibitor (0.98 M) identical to those described above. In the presence of inhibitor **26**, only slight inhibition was observed ($\epsilon = 0.07$, $K_{\text{in}} = 7.7 \times 10^{-2} \text{ M}^{-1}$), whereas with inhibitor **27**, $\epsilon = 0.16$ and $K_{\text{in}} = 0.20 \text{ M}^{-1}$. This result indicates that the complex sterically matched for the Diels–Alder reaction (**28**, eq 24), with chiral substituents on the same side of the plane defined by the square-planar metal geometry, is thermodynamically less stable than the corresponding mismatched complex **29** (eq 25).



Competitive inhibitors that more closely resemble reactants are also of interest. When standard kinetics runs (conditions specified above) were performed in the presence of inhibitors **30** and **31**, rates of reaction are suppressed, resulting in ϵ 's of 0.16 and 0.24, respectively. The binding constants K_{in} of imides **30** and **31** (0.20 and 0.33 M^{-1} , respectively) may roughly represent the affinity of an analogous crotonate dienophile for the catalyst.



Is the two-point binding nature of the products responsible for the observed inhibition? An interesting way to address this question is to directly compare one-point and two-point binding cases. For example, methyl acrylate is known to be a reactive one-point binding dienophile for the Diels–Alder reaction. Consequently, the adduct of methyl acrylate and cyclopentadiene (**32**) should be a good substrate to test. When Diels–Alder reactions of imide **5b** with cyclopentadiene were doped with methyl ester **32** (standard conditions, 0.48 M substrate, 0.96 M **32**), only slight inhibition ($\epsilon = 0.06$) due to the additive was observed, much less relative to product inhibition itself.

A Comparative Study. Independent studies by Corey and co-workers have demonstrated that phenyl-substituted bis(oxazoline)–metal complexes $[\text{Fe}(\text{Ph-box})]_2^+$ (**B**) and $[\text{Mg}(\text{Ph-box}^*)]_2$ (**C**) ($\text{Ph-box}^* = 5,5\text{-dimethyl-4-phenyl-bis(oxazoline)}$) are also catalysts for the Diels–Alder reaction

(Figure 1).¹³ These reactions have been postulated to proceed via bidentate substrate chelation to octahedral and tetrahedral metal centers, respectively, and to react out of an *s-cis* conformation. Our previous experience (vide supra) indicated that the optimal ligand for a given metal is determined by the geometry of the metal center. Thus, the best ligand for square-planar copper has proven to be *tert*-butyl-bis(oxazoline) **6d**, while phenyl-bis(oxazoline) **6a** is optimal for tetrahedral zinc. We thought it illustrative to undertake a comparative study to determine whether a similar pattern held for the Fe(III)- and Mg(II)-based systems. In addition, it was of interest to determine the relative tolerance of each catalyst system for β -substitution on the dienophile.

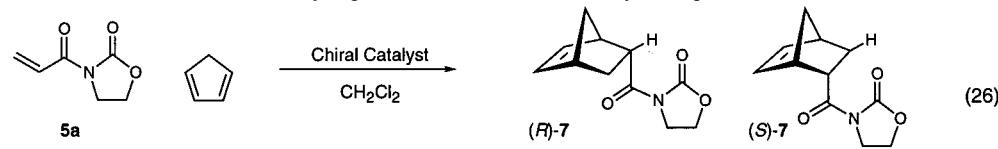
Each permutation of metal and bis(oxazoline) ligand which had been reported for the reaction was studied (eq 26, Table 8). Most notable is the fact that the *tert*-butyl ligand **6d**, which was found to be optimal for the $\text{Cu}(\text{OTf})_2$ -based catalyst, forms a poor catalyst upon complexation to Fe(III), Mg(II), or Zn(II). Similarly, phenyl-substituted ligands **6a** and **6e**, which were found to be optimal for the other metal systems, form less efficient catalysts with $\text{Cu}(\text{OTf})_2$ than does *tert*-butyl ligand **6d**.

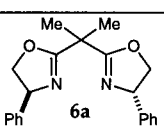
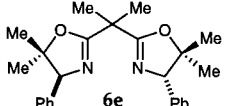
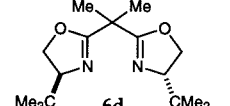
No clear explanation yet exists for the differences in behavior induced by these changes in ligand structure. However, at least one factor may account for the differences between the diphenyl ligands (**6a** and **6e**) and **6d** and their efficiencies when complexed to metals of differing geometries. It is significant to note that the *s-cis* conformation in a tetrahedral catalyst–substrate complex employing the phenyl-substituted ligands could be stabilized by an attractive π -stacking interaction which is absent when ligand **6d** is employed. In fact, if the *tert*-butyl ligand **6d** replaces the phenyl ligand **6a** in the Mg(II)- or Zn(II)-catalyzed reactions, then the resulting complexes may be destabilized sterically. Reaction from other conformations could then account for the erosion of enantioselection with this ligand. Whether analogous interactions are present in the Fe(III)-catalyzed reactions is unclear. In these systems, the larger number of potential geometries for the octahedral system complicates the analysis. Nevertheless, it is interesting to note that catalyst efficiency appears to be the result of a carefully balanced interaction between metal and ligand structure.

To gain more insight into reacting geometries, the Fe(III)-, Mg(II)-, and Zn(II)-based systems were studied in double-stereodifferentiating reactions of the type applied to the Cu(II)-based system described above. Based on the octahedral model for the Fe(III) system, and the tetrahedral model for the Mg(II) and Zn(II) systems, we hoped to observe clear matched and mismatched catalyst–dienophile complexes, as we had in the case of the Cu(II) system. However, the results preclude simple interpretation (eqs 27 and 28, Table 9).⁵⁶ In these systems, low selectivities and slow reaction rates were observed. Whether the results are due to unanticipated nonbonding interactions between the substrate benzyl groups and catalysts, or reacting geometries other than those proposed, remains an unresolved issue.

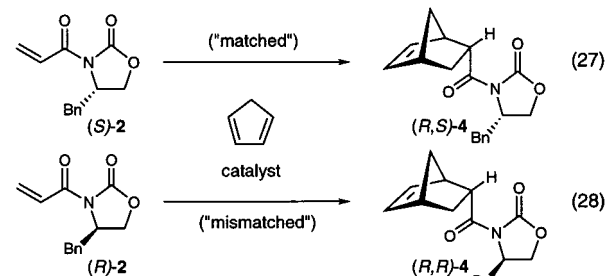
As a final point of comparison, when β -substituted dienophiles were tested with each of the four bis(oxazoline)-based catalyst systems, only the Cu(II)-based system appeared to be generally applicable (Table 10). The crotonate-derived imide **5b** was examined with each of the three catalysts (eq 29) and afforded good results when the Cu(II)-based catalysts were used [**1b** ($X = \text{SbF}_6$), *endo/exo* = 85:15, *endo ee* = 99%; **1a** ($X = \text{OTf}$), *endo/exo* = 96:4, *endo ee* = 97%]. In contrast, the Zn-

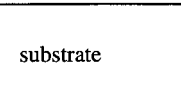
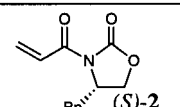
(56) These reactions, employing Zn(II) complex **8a**, were performed by Mr. Jason S. Tedrow, Harvard University.

Table 8. Diels–Alder Reaction of Imide **5a** with Cyclopentadiene and Various Catalysts (Eq 26)


catalyst (temp) ^a	L•FeI ₃ -I ₂ (-50 °C)		L•MgI ₂ -I ₂ (-78 °C)		L•Zn(SbF ₆) ₂ (-78 °C)		L•Cu(OTf) ₂ (-50 °C)	
ligand (L)	<i>endo:exo</i> ^b	<i>endo ee</i> (<i>R</i>)- 7 ^b	<i>endo:exo</i> ^b	<i>endo ee</i> (<i>R</i>)- 7 ^b	<i>endo:exo</i> ^b	<i>endo ee</i> (<i>R</i>)- 7 ^b	<i>endo:exo</i> ^b	<i>endo ee</i> (<i>S</i>)- 7 ^b
	94:6 (96:4) ^c	76 (82) ^c	94:6	76	98:2 ^c	92 ^c	95:5	30
	94:6 (95:5) ^c	82 (86) ^c	95:5 (97:3) ^c	86 (91) ^c	---- ^d	---- ^d	72:28	10
	88:12	24	94:6	0	95:5 ^e	38 ^e	97:3	98

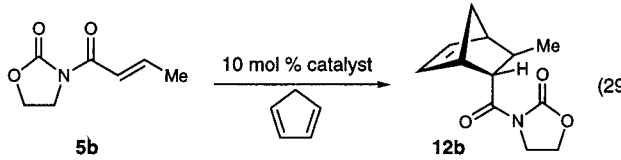
^a Reactions were run in CH₂Cl₂ with 11 mol % ligand and 10 mol % metal. ^b *Endo/exo* ratios were determined by ¹H NMR and/or chiral GLC or HPLC. Enantiomer ratios were determined either by chiral GLC or by HPLC. ^c Values in parentheses refer to literature experiments. ^d Not determined. ^e Reaction was run with Zn(OTf)₂ as metal source.

Table 9. Double-Stereodifferentiating Reactions of (*R*)-**2** and (*S*)-**2** with Cyclopentadiene Catalyzed by Various Catalysts (Eqs 27 and 28)


substrate	<i>endo:exo</i> ^b	(<i>R,S</i>)- 4 (<i>S,S</i>)- 4 ^b	<i>endo:exo</i> ^b	(<i>R,R</i>)- 4 (<i>S,R</i>)- 4 ^b
				
				
6a •FeI ₃ -I ₂ (-50 °C)	86:14	79:21	92:8	87:13
6e •MgI ₂ -I ₂ (-78 °C)	65:35	59:41	84:16	84:16
6a •Zn(SbF ₆) ₂ (-78 °C)	90:10	58:42	90:10	39:61

^a Reactions were run in CH₂Cl₂ with 11 mol % ligand and 10 mol % metal. ^b *Endo/exo* ratios and *endo/endo* II ratios were determined by ¹H NMR and/or chiral GLC or HPLC.

based catalyst provided only 64% ee (*endo/exo* = 84:16) at room temperature. At -15 °C, the Fe(III)-based system was also significantly less selective (*endo/exo* = 76:24, *endo ee* = -32%), and the Mg(II)-based system afforded racemic adducts (*endo/exo* = 4:1, *endo ee* = 0%). In addition, when we attempted to compare the three catalyst systems with respect to their efficiencies by employing the thiazolidine-2-thiones **13a–c**, we were disappointed to find that both the Fe(III)- and Mg(II)-based systems were incompatible with these substrates. Presumably, the generation of the active catalysts by employing an exogenous equivalent of I₂ (to facilitate labilization of the

Table 10. Diels–Alder Reactions of Imide **5b** with Cyclopentadiene and Bis(oxazoline)-Based Catalysts (Eq 29)^a


catalyst	time (h) ^b (temp, °C)	<i>endo/exo</i> ^c	<i>endo ee</i> (%) ^c
[Cu(<i>t</i> -Bu-box)](SbF ₆) ₂ , 1b	20 (-15)	85:15	99
[Cu(<i>t</i> -Bu-box)](OTf) ₂ , 1a	30 (-15)	96:4	97
[Zn(Ph-box)](SbF ₆) ₂ , 8a	8 (25)	86:14	-64
[Fe(Ph-box)]I ₃ •I ₂ , B	40 (-15)	76:24	-32
[Mg(Ph-box*)]I ₂ •I ₂ , C	15 (0)	80:20	0

^a Reactions were run in CH₂Cl₂ with 11 mol % ligand and 10 mol % metal. ^b Time for 100% conversion. ^c *Endo/exo* ratios were determined by ¹H NMR and/or chiral GLC or HPLC. Enantiomer ratios were determined either by chiral GLC or by chiral HPLC.

M–I bonds) creates a medium which is too highly oxidizing, resulting in decomposition of the thione dienophiles.

Conclusion. We have developed new chiral Lewis acid catalysts for the Diels–Alder reaction based on bis(oxazoline)-copper(II) complexes. The reactivity and stereoselectivity of the Cu(II) complexes were found to be profoundly influenced by the counterion. The advantages of the catalyst system presented here include high diastereo- and enantioselectivities for imide and thiazolidine-2-thione dienophiles, which have the capacity to bind to the metal center in a bidentate fashion. The low sensitivity to hydroxyl-containing additives and the efficacy of an air-stable hydrated complex provide further experimental simplicity. In addition, stereochemical probes, solid-state data, computational studies, and kinetics experiments were performed to document the intermediacy of a square-planar catalyst–substrate complex of the *s-cis*-chelated dienophile during the C–C bond forming event.

Acknowledgment. We would like to thank Professor E. N. Jacobsen for a helpful discussion regarding the kinetics study, Dr. Benjamin Anderson for useful comments, and Dr. Jeffrey Johnson for assistance in the preparation of this manuscript. Support was provided by the National Science Foundation.

Supporting Information Available: Complete experimental procedures, product characterization, and stereochemical proofs (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.
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