

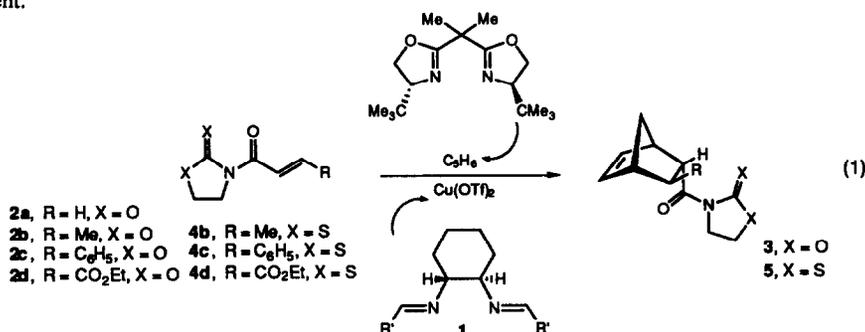
Bis(imine)-Copper(II) Complexes as Chiral Lewis Acid Catalysts for the Diels-Alder Reaction

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Abstract: We report the Diels-Alder reactions of imide-derived dienophiles **2a-2d** and **4b-4d** with cyclopentadiene catalyzed by square-planar Cu(OTf)₂-bis(imine) complexes. The 2,6-dichlorophenyl-substituted ligand **1a** was found to be generally the most effective for a range of substrates, affording products from 83-94% enantiomeric excess. Although endo:exo diastereoselectivity for the oxo-substituted imides **2a-2d** is low, significant improvement is achieved with the thiazolidine-2-thione analogues **4b-4d**, which provide enhanced dienophile reactivity and enhanced endo:exo diastereoselection.

Recent reports from this laboratory have demonstrated the efficacy of Cu(I) and Cu(II) catalysis in asymmetric cyclopropanation,² and aziridination processes.³ We have also disclosed that chiral bis(oxazoline)-Cu(OTf)₂ complexes serve as effective Lewis acids in the enantioselective Diels-Alder⁴ reactions of imides **2a-2d** and **4b-4d** with cyclopentadiene (eq 1). Prompted by the recent report by Jacobsen and co-workers that the Cu(I) complexes of bis(imine) **1** are promising aziridination catalysts,⁵ we have undertaken a study to compare the relative efficiencies of the Cu(II) complexes of these two chiral ligand families as Diels-Alder catalysts with the illustrated imide dienophiles.⁶ The bis(imine) ligands **1** are attractive since they can be readily assembled⁷ from commercially available enantiomerically pure *trans*-1,2-cyclohexanediamine and a variety of suitable aldehyde precursors, a fact which permits electronic tuning of the metal center and manipulation of the surrounding steric environment.



Catalyst Evaluation. A solution of the active catalyst can be prepared by rapidly stirring 0.9 equiv Cu(OTf)₂ and 1.0 equiv ligand **1** in CH₂Cl₂ at ambient temperature for 5 h under nitrogen to effect complexation.⁸ Initial efforts in the evaluation of these ligands involved the reaction of acrylate imide **2a** with cyclopentadiene catalyzed by a variety of substituted bis(imine)-Cu(OTf)₂ complexes derived from (-)-(*1R,2R*)-cyclohexanediamine (Table I). The highest enantiomeric excess (92%) was obtained with the 2,6-dichlorophenyl-substituted ligand **1a**, which was also the ligand of choice in the Jacobsen olefin aziridination study.⁵ The phenyl analogue **1b** afforded slightly lower endo enantioselection (85% ee) while other halogenated ligands were found to be less selective.

Table I. Reactions of Acrylate Imide **2a** with Cyclopentadiene Catalyzed by $1\cdot\text{Cu}(\text{OTf})_2$ (eq 1)^a

ligand	R' catalyst substituent	time (temp)	endo:exo ds	endo ^b ee
1a	2,6-dichlorophenyl	36 h (-78 °C)	80:20	92
1b	phenyl	36 h (-78 °C)	80:20	85
1c	4-cyanophenyl	24 h (-30 °C)	77:23	78
1d	2-chlorophenyl	36 h (-50 °C)	80:20	75
1e	2,6-difluorophenyl	36 h (-78 °C)	85:15	74
1f	4-chlorophenyl	24 h (-50 °C)	86:14	71
1g	<i>tert</i> -butyl	36 h (-78 °C)	95:5	50
1h	2,3,4,5,6-pentafluorophenyl	24 h (-78 °C)	95:5	40
1i	4-(<i>N,N</i> -dimethylamino)phenyl	36 h (-10 °C)	87:13	0

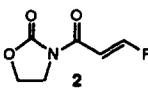
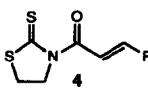
(a) Reactions run in the presence of 10 mol% ligand and 9 mol% $\text{Cu}(\text{OTf})_2$. (b) Enantiomeric ratios were determined by chiral HPLC.

The data in Table I also reveal that reaction enantioselection and endo/exo diastereoselection are independent stereochemical issues. For example, the pivaldehyde- and pentafluorobenzaldehyde-derived ligands **1g** and **1h**, while affording the highest endo selectivities (95:5), exhibited low enantioselection (40–50% ee). These results demonstrate that no apparent correlation exists between the steric bulk of the ligand, endo/exo diastereoselectivity, and endo enantioselectivity.

Scope. Ligand **1a**, whose Cu(II) complex provided the highest endo enantioselection with the acrylate imide **2a**, was chosen for further study with the illustrated imide dienophiles. The results of the catalyzed cycloaddition reactions with the selection of dienophiles are summarized in Table II. From the accumulated data, several trends are revealed. First, while the crotonate-derived imide **2b** affords good endo enantioselection (83% ee), the reaction is accompanied by poor endo/exo diastereoselectivity (65:35) (entry B). This trend is also noted for the cinnamate and fumarate derivatives **2d** and **2c** respectively (entries C, D). On the other hand, the more reactive⁹ thiazolidine-2-thione analogues **4b**, **4c** and **4d**⁴ afford significantly improved endo/exo diastereoselectivity ($\geq 90:10$) while maintaining good enantioselection, a fact which we attribute to an enhancement in two-point binding¹⁰ promoted by the elevated affinity of the C=S ligand for the metal center.

The sense of asymmetric induction for the reported reactions is stereoregular over the range of substrates examined in this study. By inspection, it is evident that the stereochemical course of the reaction is dictated by the geometry of the catalyst-dienophile complex at the metal center where the square planar and tetrahedral complexes

Table II. Enantioselective Diels-Alder Reactions of Imides **2** and **4** with Cyclopentadiene Catalyzed by $1a\cdot\text{Cu}(\text{OTf})_2$ ^a

	entry	dienophile	time (temp)	yield, % ^b	endo:exo ds	endo ^c ee	product
 2	A	2a (R = H)	30 h (-78 °C)	87	80:20	92	3a (R = H)
	B	2b (R = Me)	30 h (-10 °C)	90	65:35	83	3b (R = Me)
	C	2c (R = Ph)	84 h (25 °C) ^d	83	60:40	85	3c (R = Ph)
	D	2d (R = CO ₂ Et)	24 h (-55 °C)	98	55:45	94 ^e	3d (R = CO ₂ Et)
 4	E	4b (R = Me)	16 h (-30 °C)	86	93:7	91	5b (R = Me)
	F	4c (R = Ph)	48 h (-20 °C)	84	92:8	92	5c (R = Ph)
	G	4d (R = CO ₂ Et)	24 h (-55 °C)	99	90:10	88 ^e	5d (R = CO ₂ Et)

(a) Reactions were run in the presence of 10 mol% ligand and 9 mol% $\text{Cu}(\text{OTf})_2$. The optimal times and temperatures are provided for the indicated reactions. (b) Values refer to isolated yields of cycloadducts. (c) Enantiomer ratios were determined either by chiral GLC or chiral HPLC. (d) Fresh charges of cyclopentadiene (4 mmol) were added at the 24, 48 and 64 h marks. (e) The ee's of this cycloadduct were determined on the derived iodolactone by chiral GLC.

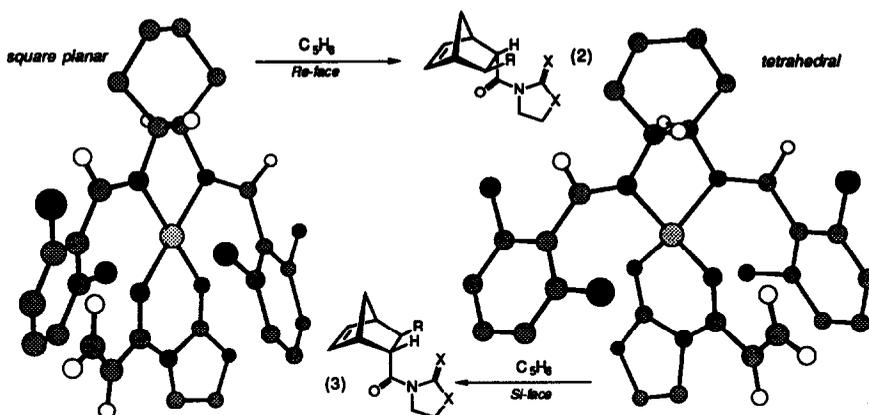
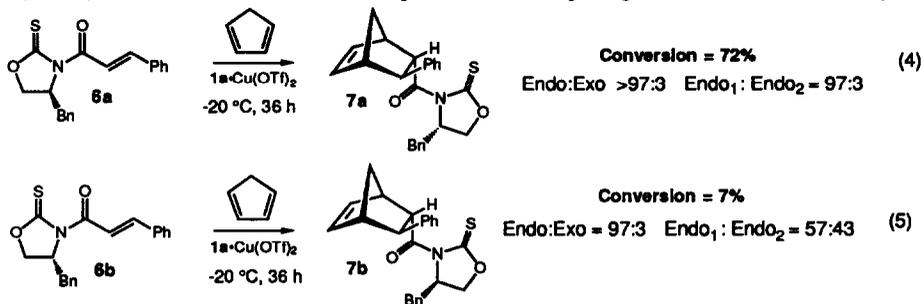


Figure 1. Square-Planar and tetrahedral catalyst-dienophile complexes and predicted face selectivities

shield opposite faces of the dienophile (Figure 1). The sense of asymmetric induction in these reactions can be rationalized by assuming that the reaction proceeds via the intermediacy of the more reasonable square-planar (eq 2) rather than tetrahedral Cu(II)-dienophile complex (eq 3).^{11,12,13}

Double Stereodifferentiating Cycloadditions. The proposed stereochemical model is supported by the following set of double stereodifferentiating reactions (eq 4, 5). The chiral oxazolidinethiones **6a** and **6b** were prepared and submitted to the standard reaction conditions optimized for the cinnamate substrate **4c** described above.¹⁴ In the "matched" case, the chirality of the ligand and the substrate have a cooperative effect, and the product **7a** was obtained with high selectivity (72% conversion; endo:exo > 97:3; endo₁:endo₂ = 97:3). However in the "mismatched" case, the stereochemical elements imposed by catalyst and substrate favor the formation of different products, and **7b** was obtained in low yield as a mixture of diastereomers (7% conversion; endo:exo = 97:3; endo₁:endo₂ = 57:43). These results are compatible with the square-planar Cu(II) coordination geometry.



We have also observed nonlinear effects in the catalytic reaction.¹⁵ When ligand **1a** of 70% ee was submitted to the standard reaction conditions with dienophile **2a**, product of 89% ee was isolated. This result is consistent with the formation of a racemic, catalytically inactive 2:1 ligand-metal complex which acts to effectively remove the minor ligand enantiomer from the system.

A comparison of the bis(imine) ligand system with that of the recently reported bis(oxazoline)-Cu(OTf)₂ catalysis of the Diels-Alder reaction⁴ reveals that enantioselectivities in the present study are on average about six points lower with comparable diastereoselectivities for the sulfur-substituted substrates. It is also significant that the oxo-substituted imide dienophiles **2a-2d** generally afford lower endo/exo diastereoselectivity than observed

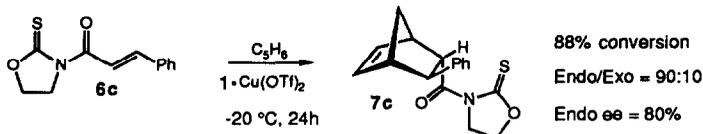
with the bis(oxazoline)-derived catalysts. Nevertheless, if the sulfur dienophile analogues **4b-4d** are employed, this stereochemical issue is largely rectified.

Additional synthetic and mechanistic studies on Cu(II) catalysis in the asymmetric Diels-Alder reaction are underway and will be reported shortly.

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References and Notes

- (1) (a) National Institutes of Health Postdoctoral Fellow (b) National Science Foundation Predoctoral Fellow
- (2) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728.
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- (4) For our results employing Bis(oxazoline) ligands in the Diels-Alder reaction, see Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460-6461.
- (5) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.
- (6) Our studies on olefin aziridination provide evidence that the active catalyst in these reactions is the Cu(II)-(ligand) complex, Ref 3.
- (7) The requisite diimine ligands can be synthesized by refluxing 1 equiv of enantiomerically pure diamine with 2 equiv of aldehyde in benzene with azeotropic removal of water, followed by concentration and recrystallization of the resulting solid from varying proportions of ethyl acetate:hexane.
- (8) A representative procedure follows: Cu(OTf)₂ (Aldrich, 32.5 mg, 0.09 mmol) was added to a solution of ligand **1a** (43 mg, 0.1 mmol in 2.0 mL CH₂Cl₂) at room temperature under nitrogen. Vigorous stirring was continued for 5 h, forming a homogeneous but slightly cloudy purple-blue solution of the ligand complex. Dienophile (1 mmol) was added at -78 °C, followed by cyclopentadiene (10 mmol). The reaction pot was maintained at the isotherm for the specified time, diluted with ether, and filtered through a small plug (1 cm X 2 cm) of silica gel. The plug was washed repeatedly with ether (3 X 10 mL) to ensure elution of the product. Analysis of the crude reaction mixture was performed by HPLC on a Daicel Chiralcel® column. Chromatography on silica yielded the pure Diels-Alder adducts.
- (9) Competition experiments have established that the sulfur analogues **4b-4d** are 20-30 times as reactive as their oxygen counterparts **2b-2d**, Ref 4.
- (10) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.
- (11) For the sake of the ensuing analysis, it is assumed without corroborating evidence, that both triflate ligands are dissociated from the metal center. For an X-ray structure of the related **1c**-Cu(I)OTf complex see: Evans, D. A.; Woerpel, K. A.; Scott, M. S. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430-432.
- (12) The structures in Figure 1 are Chem 3D representations.
- (13) For a discussion on the coordination chemistry of Cu(II), see: Hathaway, B. J. In *Comprehensive Coordination Chemistry*, Wilkinson, G; Gillard, R. D.; McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1989; Vol. 5, pp 533-750.
- (14) Initially the double stereodifferentiating reactions were explored with chiral oxazolidinone derived imides. However the low diastereoselectivity of the process complicated the analysis. The achiral oxazolidinethione **6c** affords cycloadducts with improved diastereoselectivity relative to the oxo-case.



- (15) For examples of documented non-linear effects in asymmetric catalysis, see: Puchot, C.; Samuel, O.; Dunach, É.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353-2357. Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69.