Bis(oxazoline) and Bis(oxazolinyl)pyridine Copper Complexes as Enantioselective Diels−Alder Catalysts: Reaction Scope and Synthetic Applications

David A. Evans,* David M. Barnes, Jeffrey S. Johnson, Thomas Lectka, Peter von Matt, Scott J. Miller, Jerry A. Murry, Roger D. Norcross, Eileen A. Shaughnessy, and Kevin R. Campos

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received April 14, 1999

Abstract: The scope of the Diels−Alder reaction catalyzed by bis(oxazoline) copper complexes has been investigated. In particular, [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**1b**) has been shown to catalyze the Diels−Alder reaction between 3-propenoyl-2-oxazolidinone (**2**) and a range of substituted dienes with high enantioselectivity. This cationic complex has also been employed in the catalysis of analogous intramolecular processes with good success. The total syntheses of *ent*-Δ^1-tetrahydrocannabinol, *ent*-shikimic acid, and isopulo'upone, featuring the use of this chiral catalyst in more complex Diels−Alder processes, are described. Similarly, the cationic copper complex **9a**, [Cu((*S*,*S*)-*t*-Bu-pybox)](SbF$_6$)$_2$, is effective in the Diels−Alder reactions of monodentate acrolein dienophiles while the closely related complex, **9d** [Cu((*S*,*S*)-Bn-pybox)](SbF$_6$)$_2$, is the preferred Lewis acid catalyst for acrylate dienophiles in reactions with cyclopentadiene.

Introduction

Remarkable progress has been made in the development of chiral Lewis acids as catalysts for enantioselective Diels−Alder reactions.[1] A number of systems have been reported that provide excellent levels of selectivity; however, many of these are limited in scope, such that only a handful of reacting partners are accessible. For one to take full advantage of this powerful transformation, more reactive catalysts are needed which provide greater flexibility in the nature of the diene, as well as in the substitution pattern on the dienophile. Previous reports from this laboratory described the development of copper-based Lewis acids as catalysts for enantioselective Diels−Alder[2] reactions.[3,4] These studies have demonstrated that [Cu((*S*,*S*)-*t*-Bu-box)]- (SbF$_6$)$_2$ (**1b**) is an excellent catalyst for reactions between cyclopentadiene and acrylimide **2** and substituted analogues thereof (R = Me, Ph, CO$_2$Et),[5] affording cycloadducts **3** with

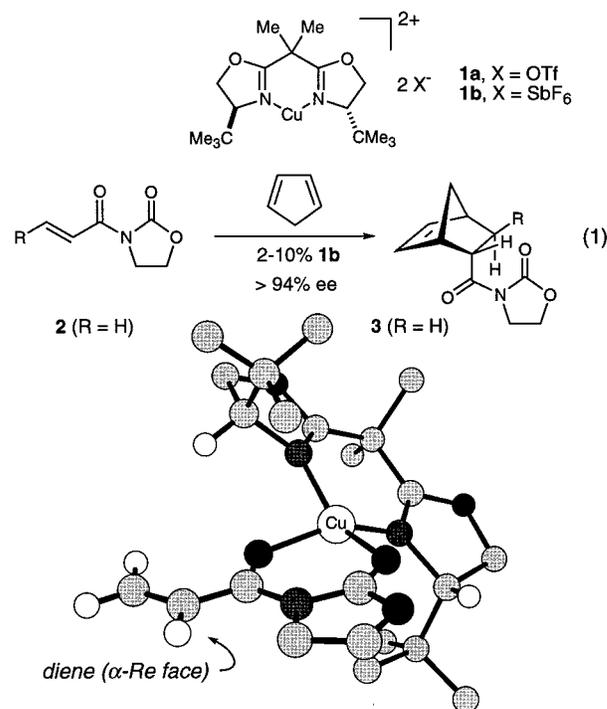$$ \text{(1)} $$

2 (R = H)　　　　　　　**3** (R = H)

diene (α-Re face)

Figure 1. PM-3-generated [Cu((*S*,*S*)-*tert*-Bu-box)](2+) complex **1b** bound to acrylimide **2** (ref 2d).

enantioselectivities in excess of 94% at ambient temperatures (eq 1).[2] Mechanistic investigations support a scenario of dienophile activation via bidentate coordination to a distorted square planar copper center, a model that is consistent with the absolute stereochemical outcome of all reactions investigated to date (Figure 1). X-ray and computational structures of relevant complexes have corroborated this model.[6]
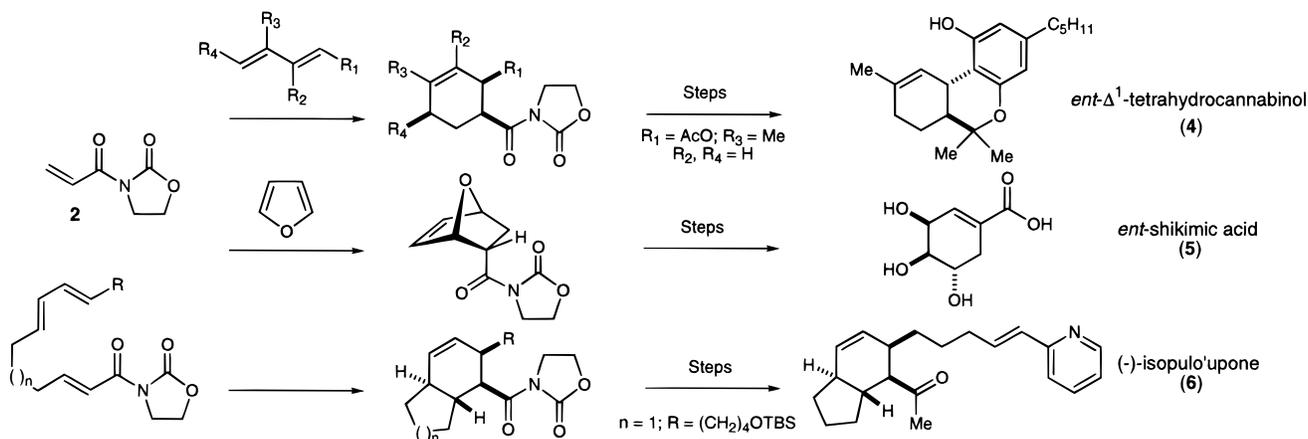
(1) For reviews see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007−1020. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741−761. (c) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332. (d) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763−784. (e) Maruoka, K.; Yamamoto, H. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 413−440. (f) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1993; pp 212−217. (g) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129−158. (h) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

(2) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027−7030. (c) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (d) Previous paper, this issue.

(3) For the use of these complexes in Mukaiyama aldol reactions see: (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685 and references therein. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699 and references therein.

(4) For the relative effectiveness of chiral Lewis acids derived from Cu-(II) and Zn(II), see: Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484.

Bis(oxazoline) and Bis(oxazolinyl)pyridine

J. Am. Chem. Soc., Vol. 121, No. 33, 1999 7583

Scheme 1

Among the systematically developed chiral Lewis acid complexes, only the [Ti(TADDOL)]Cl$_2$ catalysts have been regularly employed in reactions of imide dienophiles with dienes other than highly reactive cyclopentadiene derivatives.[7] Likewise, only these complexes have been used to promote intramolecular Diels–Alder reactions of imides.[8] Indeed, despite notable progress in the development of chiral Lewis acid catalysts, few are sufficiently activating to promote the Diels–Alder reactions either of more heavily substituted acyclic dienes[9] or of their intramolecular variants.[10]

In the present investigation, the scope and synthetic utility of [Cu((*S,S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**1b**) in the catalysis of both intra- and intermolecular imide-based Diels–Alder reactions are described (Scheme 1).[2a,2d,4] Included in this study are the

asymmetric syntheses of *ent*-Δ^1-tetrahydrocannabinol (**4**), *ent*-shikimic acid (**5**), and (−)-isopulo'upone (**6**).[11] In the second part of this study, the cationic Cu(II) complexes **8** and **9**, derived from the readily accessible bis(oxazolinyl)pyridyl (pybox) ligand family 7,[12] are evaluated as chiral catalysts for Diels–Alder reactions with acrolein, methacrolein, bromoacrolein, and acrylate ester dienophiles that are activated by single-point catalyst coordination (eqs 2, 3).[2c] The results of this and other studies indicate that these complexes are effective catalysts not only for the Diels–Alder reaction but also for other processes.[13]
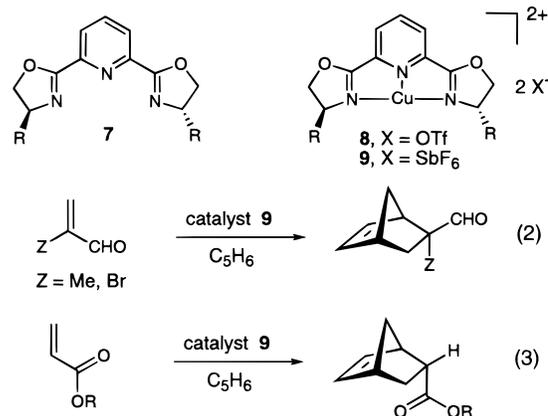
Results and Discussion

[Cu((*S,S*)-*t*-Bu-box)](SbF$_6$)$_2$-Catalyzed Cycloadditions. (A) Catalyst Preparation. Solutions of the triflate complex [Cu-((*S,S*)-*t*-Bu-box)](OTf)$_2$ (**1a**) were prepared by stirring (*S,S*)-*tert*-butyl-bis(oxazoline) (**10**)[14] with Cu(OTf)$_2$ in CH$_2$Cl$_2$ at room temperature for 2–4 h (eq 4). In early work,[2c,2d] the analogous hexafluoroantimonate catalyst [Cu((*S,S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**1b**) was prepared by vigorously stirring the ligand **10**, CuCl$_2$, and

(5) Several other catalysts have also been reported to provide good to excellent enantioselectivities in the reactions of cyclopentadiene with **2** and with β-substituted acrylimides (R ≠ H). **Al**: (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493−5495. **Yb, Sc**: (b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535−4538. (c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083−4084. (d) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623−11636. (e) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett.* **1999**, *40*, 1555−1558. **Zr**: (f) Jaquith, J. B.; Levy, C. J.; Bondar, G. V.; Wang, S. T.; Collins, S. *Organometallics* **1998**, *17*, 914−925 and references therein. **Cu**: (g) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3687−3691 and references therein. (h) Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261−264. **Ni**: (i) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088 and references therein. **Zn**: (j) Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3079−3087 and references therein.

(6) (a) ref 3b. (b) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3372−3375.

(7) (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345, and references therein. (b) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289− 6292. (c) Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387−391. (c) Narasaka, K.; Yamamoto, I. *Tetrahedron* **1992**, *48*, 5743− 5754. (d) Yamamoto, I.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3327−3333. (e) Yamamoto, I.; Narasaka, K. *Chem. Lett.* **1995**, 1129−1130. (f) Tietze, L. F.; Ott, C.; Frey, U. *Liebigs Ann. Chem.* **1996**, 63−67.

(8) (a) Iwasawa, N.; Sugimori, J.; Kawase, Y.; Narasaka, K. *Chem. Lett.* **1989**, 1947−1950. (b) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron: Asymmetry* **1991**, *2*, 1305−1318.

(9) For recent examples, see: (a) Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502−5503. (b) Bruin, M. E.; Kündig, E. P. *Chem. Commun.* **1998**, 2635−2636. (c) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820. (d) Yamamoto, H.; Ishihara, K. *J. Am. Chem. Soc.* **1994**, *116*, 1561−1562. (e) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049−3050. (f) Reference 5g. (g) Ishihara, K.; Gao, Q. Z.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917−6919 and references therein. (h) Corey, E. J.; Guzman-Perez, A.; Loh, T. P. *J. Am. Chem. Soc.* **1994**, *116*, 3611−3612 and references therein.

(10) (a) References 8 and 9e. (b) Furuta, K.; Kanematsu, A.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231−7232.

(11) A portion of this work has been communicated. (a) Reference 2c. (b) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57−58. (c) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. (d) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193−3194.

(12) (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224 and references therein. (b) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−508. The experimental procedure for the synthesis of the pybox ligand may be found in this paper.

(13) For the application of these complexes to the catalysis of the aldol reaction, see ref 3.

(14) For the synthesis of (*S,S*)-*tert*-butyl bis(oxazoline) (**10**), see Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

AgSbF$_6$ together in CH$_2$Cl$_2$ for 8–16 h; the AgCl precipitate was removed by filtration through Celite to provide the active catalyst solution. While catalyst solutions thus generated provided high enantioselectivities, for operational convenience an alternative and more reliable catalyst preparation has been developed. Equimolar amounts of the bis(oxazoline) **10** and the insoluble brown anhydrous CuCl$_2$ were stirred in CH$_2$Cl$_2$ over a period of 3 h, during which time a green solution of [Cu-((*S,S*)-*t*-Bu-box)]Cl$_2$ complex **11** was formed. This complex may be isolated as its CH$_2$Cl$_2$ solvate in 99% yield after filtration and concentration.[15] This green powder can be stored indefinitely at room temperature without decomposition. The active catalyst solution was obtained by treating **11** with 2 equiv of AgSbF$_6$ in CH$_2$Cl$_2$ for 3–4 h to afford [Cu((*S,S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**1b**) (eq 5). Filtration of the catalyst solution through Celite was performed in the atmosphere. This catalyst preparation proved to be operationally convenient and reproducible.
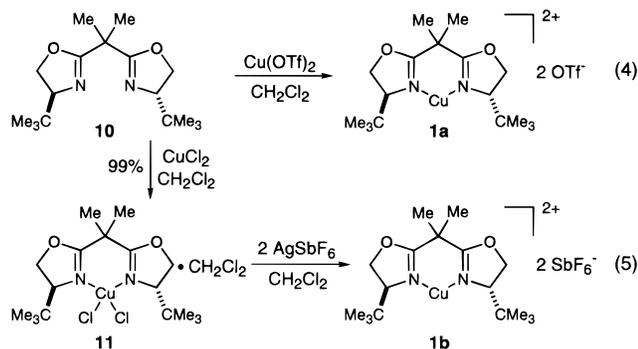
(B) Alkyl-Substituted Dienes. With the high catalytic activity of bis(oxazoline) copper complexes **1a** and **1b** established in the Diels−Alder reactions of cyclopentadiene, attention was directed to less reactive dienes, such as cyclohexadiene (Table 1, eq 6). Not unexpectedly, this reaction also exhibited a significant counterion effect.[16] While 10 mol % of triflate catalyst **1a** required 40 h to promote the reaction to complete conversion at room temperature (82% ee, entry 1), the SbF$_6$ complex **1b** displayed substantially greater catalytic potency and selectivity, requiring only 5 h at the same temperature (93% ee, entry 2) for complete conversion.[17] The observation that **1a** (X = OTf) afforded higher diastereoselectivity (endo/exo = 98: 2) was consistent with earlier observations, although the decrease in diastereoselectivity with SbF$_6$ catalyst **1b** (endo/exo = 95:5) was not as pronounced as in the corresponding reaction of cyclopentadiene (**1a**, endo **3**/exo **3** = 98:2; **1b**, endo **3**/exo **3** = 91:9).[2c] The temperature dependence of the SbF$_6$ catalyst **1b** (25 °C, 93% ee; −10 °C, 95% ee) is low, and the decrease in reaction rates at the lower temperatures is usually the determining issue in the selection of a given reaction temperature.

The enantioselectivity of the reaction between imide **2** and cyclohexadiene erodes significantly when the catalyst loading is lowered (Table 1, eq 6). In this respect, the cycloaddition with cyclohexadiene was not as tolerant as the corresponding reaction with cyclopentadiene.[2c] With 5 mol % of catalyst **1b** (X = SbF$_6$), adduct **12** was formed in 89% ee after 40 h at 25 °C (95% conv.; entry 4). Further reduction of catalyst to 2 and 1 mol % resulted in yet lower conversion and diminished

(15) The X-ray structure of [Cu((*S,S*)-*tert*-Bu-box)]Cl$_2$·CH$_2$Cl$_2$ has been solved. See ref 2d.

(16) A counterion study was performed as in the previous paper (ref 2d). As observed in that study, the order of reactivity of the counterions was SbF$_6$ > PF$_6$ > BF$_4$ > OTf.

(17) The corresponding reactions with cyclopentadiene required 10 h (catalyst **1a**) and <4 h (catalyst **1b**) at −78 °C. Reference 2c.

Table 1. Reaction of **2** with Cyclohexadiene Catalyzed by **1** (eq 6)^a
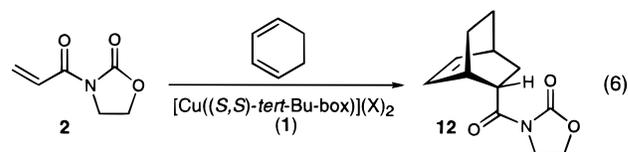
catalyst	mol %	temp (time)	endo/ exo^b	endo ee^c	yield^d
1a (X = OTf)	10	25 °C (40 h)	98:2	82% ee	90%
1b (X = SbF$_6$)	10	25 °C (5 h)	95:5	93% ee	90% (97%)
1b (X = SbF$_6$)	10	−10 °C (46 h)	96:4	95% ee	49%
1b (X = SbF$_6$)	5	25 °C (40 h)	95:5	89% ee	(95%)
1b (X = SbF$_6$)	2	25 °C (40 h)	95:5	80% ee	(78%)
1b (X = SbF$_6$)	1	25 °C (40 h)	95:5	74% ee	(65%)

^{a} Reactions run in CH$_2$Cl$_2$ with 10 equiv of diene. ^{b} Diastereomer ratios determined by ^{1}H NMR. ^{c} Enantiomer ratios determined by chiral HPLC on the derived α-methylbenzyl amide. Major product absolute stereochemistry assumed in analogy to **3**. ^{d} Values refer to isolated yields of cycloadducts. Numbers in parentheses refer to percent conversion (GLC).

enantioselectivities of 80% and 74% ee, respectively (entries 5 and 6). The competing uncatalyzed thermal Diels−Alder reaction between imide **2** and cyclohexadiene at 25 °C afforded 1% conversion to adduct **12** after 5 h and 7% conversion after 40 h, indicating that the erosion in enantioselectivity observed with a lower catalyst concentration is not solely due to the background reaction.

Complexes **1a** (X = OTf) and **1b** (X = SbF$_6$) were also found to catalyze cycloadditions between imide **2** and representative acyclic dienes (Table 2). As in the case of cyclohexadiene, the SbF$_6$ catalyst generally provided higher selectivities and significantly shorter reaction times than the triflate derivative. When **1a** (X = OTf) was employed, the reaction of piperylene with imide **2** yielded a mixture of all eight possible stereo- and regioisomers. The major cis regioisomer **13**, accounting for 75% of the product mixture, was formed in 86% ee (Table 2, entry 1). Recrystallization of the product mixture provided enantiomerically pure material. When the reaction was repeated with catalyst **1b** (X = SbF$_6$), cycloadduct **13** was formed in 94% ee and accounted for 83% of the product mixture (entry 2). Similarly, *trans,trans*-2,4-hexadiene underwent a highly enantioselective Diels−Alder reaction with imide **2** at room temperature. Catalyst **1a** (X = OTf) afforded product **14** as a 78: 22 mixture of cis and trans isomers, and the cis product was formed in 84% ee (entry 3). Catalyst **1b** (X = SbF$_6$) provided almost the same diastereoselectivity, while the reaction enantioselectivity rose to 93% (entry 4).

The reaction between acrylimide **2** and 1-phenylbutadiene was also investigated.[18] When 10 mol % of catalyst **1a** (X = OTf) was employed at room temperature, the product was isolated in 89% yield as a 2:1 mixture of cis and trans cycloadducts with the cis isomer **15** being formed in 84% ee (entry 5). When catalyst **1b** (X = SbF$_6$) was employed at room temperature, the metal center was reduced by the diene, resulting in precipitation of metallic copper. However, when the reaction was carried out at −20 °C, catalyst reduction was avoided, permitting isolation of the product in 95% yield as a 85:15 mixture of cis/trans isomers, with the cis product formed in 97% ee (entry 6). The reduction of catalyst **1b** by 1-phenylbutadiene at room temperature highlights the effect of the SbF$_6$ counterions
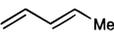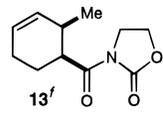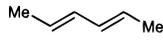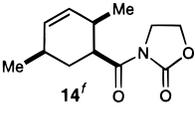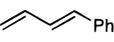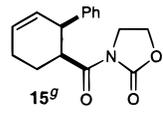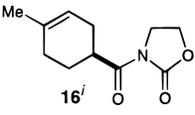
(18) Grummitt, O.; Becker, E. I. *Organic Syntheses, Collective Volume IV*; Rabjohn, N., Ed.; Wiley: New York, 1963; pp 771−775.

Table 2. Diels−Alder Reactions of Imide **2** with Various Dienes Catalyzed by [Cu((S,S)-*tert*-Bu-box)]X₂ (**1**)[a]

Diene	entry	catalyst	temp	time	cis:trans[b]	cis ee[c]	yield[d]	major product
	1	**1a** (X = OTf)	25 °C	12 h	75:25[e]	86% ee	72%	**13**[f]
	2	**1b** (X = SbF₆)	25 °C	12 h	83:17[e]	94% ee	89%	
	3	**1a** (X = OTf)	25 °C	36 h	78:22	84% ee	66%	**14**[f]
	4	**1b** (X = SbF₆)	25 °C	12 h	77:23	93% ee	59%	
	5	**1a** (X = OTf)	25 °C	24 h	67:33	84% ee	89%	**15**[g]
	6	**1b** (X = SbF₆)	-20 °C	24 h	85:15	97% ee	95%	
	7	**1a** (X = OTf)	25 °C	24 h	97:3[h]	60% ee	95%	**16**[i]
	8	**1b** (X = SbF₆)	25 °C	12 h	96:4[h]	59% ee	81%	
	9	**1a** (X = OTf)	25 °C	24 h	--	60% ee	95%	**17**[f]
	10	**1b** (X = SbF₆)	25 °C	24 h	--	65% ee	78%	
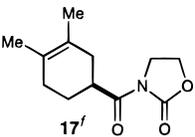
[a] Reactions run in CH₂Cl₂ with 10 mol % catalyst and 10 equiv of diene. [b] Diastereomer ratios determined by ¹H NMR, or chiral GLC or HPLC. [c] Enantiomer ratios determined by chiral GLC or chiral HPLC on the primary adduct or on the corresponding α-methylbenzyl amides or ethylthioesters. See Experimental for details. [d] Values refer to isolated yields of cycloadducts. [e] Ratio refers to major cis: Σ other isomers. [f] Major product absolute stereochemistry assumed in analogy to cycloadducts **15** and **16**. [g] Absolute stereochemistry assigned by independent synthesis. See text for details. [h] Values refer to (1,4):(1,3) regioisomer ratio. [i] Major product stereochemistry proved by correlation to the benzyl ester derived from the cycloadduct obtained from the Al-mediated reaction of a chiral dienophile. Reference 20.

in raising the Lewis acidity and, therefore, the reduction potential of this catalyst.[19] Fortunately, temperature control may be effectively employed to contain this side reaction.

A decrease in enantioselectivity was noted with those dienes which are not substituted at the 1-position. Both isoprene and 2,3-dimethylbutadiene exhibited good reactivity, yet in each case the enantiomeric excess of the major cycloadduct was lower than those observed for other dienes. The isoprene-derived 1,4-regioisomer **16** was isolated in up to 64% ee (1,4:1,3 selectivity ≥ 96:4, entries 7 and 8), and the 2,3-dimethylbutadiene-derived cycloadduct **17** was obtained in up to 65% ee (entries 9 and 10). The absolute stereochemistry of cycloadduct **16** was determined by conversion to the known benzyl ester.[20]

The reason for the attenuated enantioselectivity in reactions of isoprene and 2,3-dimethylbutadiene is unclear; however, we postulate that steric interactions between the substituent methyl groups and the catalyst lead to reaction largely via an exo transition state. Supporting this hypothesis, we have found that the catalyzed reaction of 1-acetoxybutadiene is endo-selective (85:15) while that of 1-acetoxy-3-methylbutadiene favors the exo product (73:27, vide infra). Furthermore, 1-vinylcyclohexene provides a 1:1 mixture of endo and exo products (enantioselectivities not determined). If the exo approach of dienes unsubstituted at the 1-position is relatively nonselective, this would explain the low enantioselectivities in entries 7−10. A more detailed discussion of the effect of diene substituents on reaction diastereoselectivity and enantioselectivity will be presented later (vide infra).

The reaction of 1-phenylbutadiene with imide **2** was chosen for further optimization. Whereas the above reactions were

(19) 1-(Tri-*n*-butylstannyl)butadiene (Gómez, A. M.; López, J. C.; Frasier-Reid, B. *Synthesis* **1993**, 943−944.) was subjected to the copper catalyzed Diels−Alder reaction and was also found to reduce the catalyst rapidly at −25 °C.

(20) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

performed at an imide concentration of 0.2−0.3 M, it was found that concentrations as high as 0.5 M afforded equivalent results.[21] Under these conditions, only 2 mol % catalyst was required to promote the reaction to complete conversion in 13 h. Scale-up proceeded without incident; a 50 mmol scale reaction yielded enantiomerically and diastereomerically pure cis cycloadduct **15** in 80% yield after recrystallization (eq 7).

(7)

2 (50 mmol)

15
>99% ee, one diastereomer
80% isolated
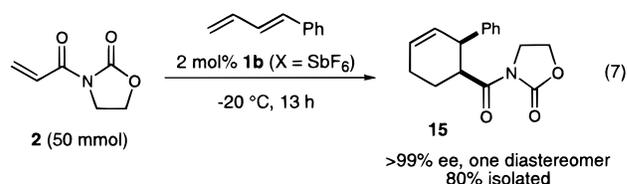
To assay the selectivity of this reaction, we converted the initially formed imide cycloadduct mixtures to the *S*-ethyl thioesters by treatment with LiSEt (0 °C, THF).[22] Enantiomer and diastereomer ratios were then determined by chiral HPLC analysis. During the course of this study, it was found that prolonged exposure of the cis thioester **18** to LiSEt resulted in equilibration to the derived trans isomer. Thus, cis imide **15** could be cleaved under either kinetic conditions to provide cis thioester **18** (98:2, eq 8) or thermodynamic conditions to provide the trans isomer **19** with excellent selectivity (95:5, eq 9). The absolute stereochemical assignment of the 1-phenylbutadiene cycloadduct was established by independent synthesis of cis thioester **18** (eq 10). Lewis acid-mediated reaction of chiral acrylate imide **20**[20] and 1-phenylbutadiene delivered crystalline adduct **21** (mp >180 °C), whose relative stereochemistry was established by X-ray analysis. Thiolate cleavage (LiSEt, THF,
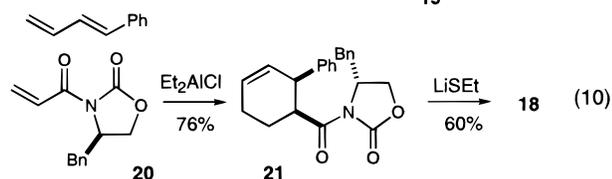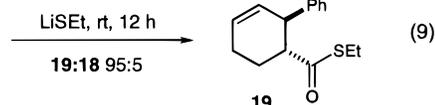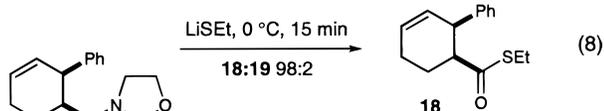
(21) The imide was insoluble at −20 °C at higher concentrations.

(22) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1988**, *29*, 6141−6144.

0 °C, 2 h) provided thioester **18**, which was identical to material derived from the catalyzed reactions.

(C) Heteroatom-Substituted Dienes. The [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ complex (**1b**) was then evaluated as a catalyst in reactions with heteroatom-substituted dienes (eq 11, X = OAc, SPh, NHCbz). As with 1-phenylbutadiene, these dienes are sensitive to oxidation by the catalyst, and to polymerization, and the indicated reaction temperatures for these substrates represent the highest temperature that the reactions may be run without incurring these side reactions.

1-Acetoxybutadiene[23] undergoes a clean reaction with acrylimide **2** at 0 °C to yield adduct **22a** (X = OAc) (eq 11, Table 3).[24] When run with 5 mol % catalyst, the reaction proceeded

Table 3. The Diels−Alder Reaction of Imide **2** with 1-Heteroatom-Substituted Butadienes (eq 11)[a]
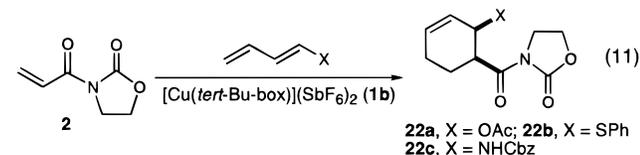
| entry	diene	mol % **1b**	time (temp)[b]	cis/ trans[c]	cis ee[c]	yield[d]
1	X = OAc	5%	<23 h (0 °C)	85:15	98%[e]	nd
2	X = OAc	2%	24 h (0 °C)	85:15	96%[e]	75%
3	X = OAc	1%	48 h (0 °C)	85:15	95%[e]	nd
4	X = SPh	2%	24 h (−20 °C)	98:2	98%[f]	84%
5	X = NHCbz	5%	24 h (0 °C)	72:28	90%[g]	54%

[a] Reactions were carried out in CH$_2$Cl$_2$ with 5 equiv of diene. [b] Time required for complete conversion. [c] Diastereomer ratios and enantiomeric excesses were determined by chiral HPLC. [d] Values refer to isolated yields of cis adducts. [e] Ee of the trans isomer was 90%. [f] Ee of the trans isomer was 89%. [g] Ee of the trans isomer was 97%.

to completion in less than 24 h at 0 °C to provide the product as an 85:15 mixture of cis:trans isomers; the cis isomer was formed in 98% ee. Reaction with 2 mol % catalyst required 24 h, and the enantioselectivity was only slightly eroded (entry 2). In fact, the product was formed in 95% ee after 48 h when employing only 1 mol % of the catalyst (entry 3). The cis adduct could be isolated from these reaction mixtures in 75% yield by chromatography. These results are especially significant as the Me$_2$AlCl-promoted reaction of 1-acetoxybutadiene with chiral acrylimide **20** failed to provide any cycloadduct.

(23) Bailey, W. J.; Barclay, R. *J. Org. Chem.* **1956**, *21*, 328−331.
(24) Diels−Alder reactions of 1-acetoxybutadiene with methacrolein and juglone have been reported. See ref 9c.

The relative stereochemistry of **22a** (X = OAc) was determined by conversion to the crystalline ammonium carboxylate derivative **24** (eq 12). Treatment of the major isomer **22a** with LiOOH[25] under carefully monitored conditions (THF, −5 °C, 15 min) selectively effected imide hydrolysis to provide acid **23** in 85% yield. Treatment of **23** with dicyclohexylamine in CH$_2$Cl$_2$ provided crystalline dicyclohexylammonium salt **24**, which was assigned the cis stereochemistry by X-ray analysis.
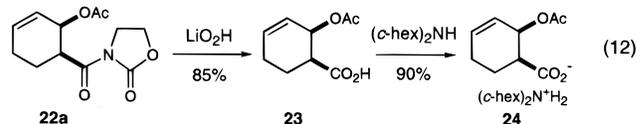

The reaction of imide **2** with 1-phenylthiobutadiene,[26] employing 2 mol % SbF$_6$ catalyst **1b** at −20 °C, afforded cycloadduct **22b** (X = SPh) with high endo selectivity (Table 3, entry 4, cis/trans = 98:2; cis ee = 98%). The cis isomer was obtained diastereomerically and enantiomerically pure in 84% yield by recrystallization. An X-ray structure of the product confirmed both relative and absolute stereochemistry.

1-(Benzyloxycarbonylamino)butadiene[27] also underwent reaction with imide **2**. In this case, 5 mol % of catalyst **1b** was required; cycloadduct **22c** (X = NHCbz) was obtained as a 72:28 mixture of cis/trans isomers, from which the cis isomer was isolated in 54% yield and in 90% ee (Table 3, entry 5). It appears likely that the Lewis basic carbamate group associates with the metal center of complex **1b**,[28] attenuating its Lewis acidity and requiring the higher catalyst loading. The cis stereochemistry of cycloadduct **22c** (X = NHCbz) was assigned by X-ray analysis of racemic product obtained via a thermal reaction.

Synthesis of *ent*-Δ^1-Tetrahydrocannabinol (4). On the basis of the results obtained with 1-acetoxybutadiene, we designed an asymmetric synthesis of the cannabinols (Scheme 2). In this

Scheme 2
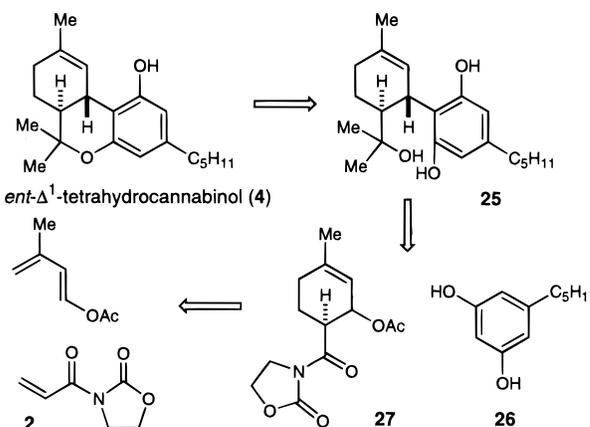
route, triol **25**, the cyclization precursor to *ent*-Δ^1-tetrahydrocannabinol (**4**) arises via an acid- or metal-mediated addition of olivetol (**26**) to the allylic oxygen functionality present in cycloadduct **27**, in turn derived from the catalyzed Diels−Alder reaction of acrylimide **2** with 1-acetoxy-3-methylbutadiene.

(25) Evans, D. A.; Ellman, J. A.; Britton, T. C. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.
(26) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208−1217.
(27) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164−2167.
(28) Evidence for N-coordination of amides has been reported. See: Cox, C.; Ferraris, D.; Murthy, N. N.; Lectka, T. *J. Am. Chem. Soc.* **1996**, *118*, 5332−5333.

Bis(oxazoline) and Bis(oxazolinyl)pyridine

J. Am. Chem. Soc., Vol. 121, No. 33, 1999 7587

The reaction of 1-acetoxy-3-methylbutadiene[29] and imide **2** catalyzed by **1b** (2 mol %, CH$_2$Cl$_2$, −20 °C, 18 h) afforded cycloadduct **28** as a 73:27 mixture of diastereomers from which the major diastereomer, initially formed in 98% ee, was isolated enantiomerically pure by direct crystallization (mp 124−5 °C, eq 13).[30] When the reaction was performed on a 50 mmol scale, **28** crystallized from the unpurified reaction mixture, yielding 57% of enantiomerically and diastereomerically pure material. An X-ray structure of adduct **28** established the anti relative stereochemistry of the major diastereomer, formed via an exo transition state. The stereochemical outcome of this reaction is clearly opposite to that anticipated and will be discussed later (vide infra).

(13)

2 (50 mmol)

2 mol% **1b**
-20 °C, 18 h

trans:cis 73:27
98% ee, 57% yield

28
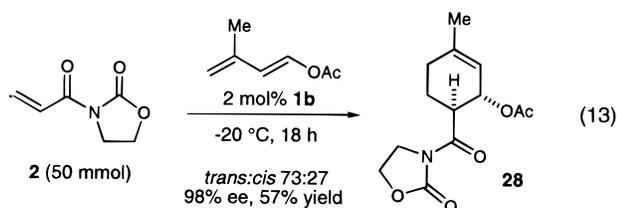
Addition of LiOBn to cycloadduct **28** (6 equiv of LiOBn, 0 °C) effected transesterification of both imide and acetate moieties to afford β-hydroxy ester **29** in 78% yield (Scheme 3); however, this product proved difficult to separate from excess

Scheme 3[a]

ent-Δ^1-tetrahydrocannabinol (**4**)

25
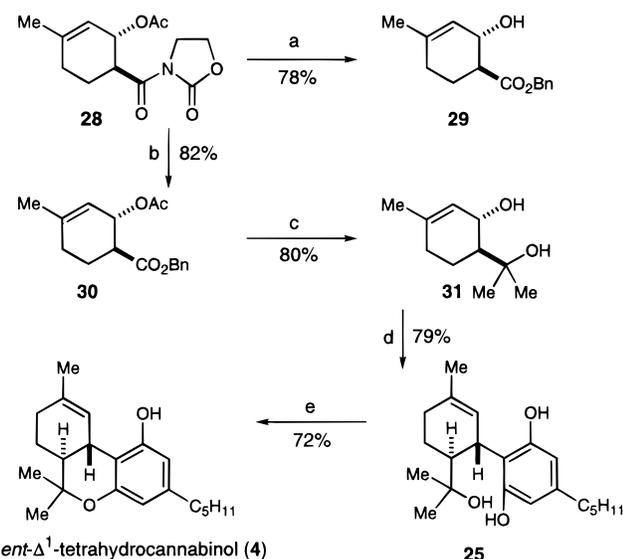
[a] (a) Six equivalents of LiOBn, THF, 0 °C, 2.5 h; (b) 2 equiv of LiOBn, THF, −20 °C, 3 h; (c) 6 equiv of MeMgBr, ether, 0 °C, 2 h; (d) **26**, *p*-TSA, CH$_2$Cl$_2$, 0 °C, 7 h; (e) ZnBr$_2$, MgSO$_4$, CH$_2$Cl$_2$, 20 °C, 5 h.

benzyl alcohol. Alternatively, selective imide cleavage was achieved under less forcing conditions (2 equiv of LiOBn, −20 °C) to provide ester **30** in 82% yield. Addition of excess methylmagnesium bromide to **30** provided allylic alcohol **31** (80%). Acid-catalyzed alkylation of olivetol with **31** at high

dilution (0.003 M in CH$_2$Cl$_2$, *p*-toluenesulfonic acid, *p*-TSA) afforded the cyclization substrate **25** in good yield (79%).[31] The synthesis was then completed through the precedented[31,32] ZnBr$_2$-promoted cyclization of **25** which was modified by the addition of MgSO$_4$. The product mixture was easily purified by flash chromatography to provide a 72% yield of *ent*-Δ^1-tetrahydrocannabinol (**4**). This procedure delivered **4** free from contamination by isomeric products, which has been reported to be a problem in previous syntheses.[33] When the cyclization was performed without MgSO$_4$, an isomeric cannabinol derivative was obtained as a significant byproduct (25%). The use of *p*-TSA as the cyclization promoter resulted in the formation of significant amounts of Δ^6-tetrahydrocannabinol via double-bond isomerization. The spectroscopic data of synthetic (+)-Δ^1-tetrahydrocannabinol was identical to the published data of the natural product,[32] with the exception of the rotation, which was opposite in sign: [α]$^{25}_D$ (literature) −150 (*c* 0.53, CHCl$_3$); [α]$^{25}_D$ (synthetic) +141 (*c* 0.55, CHCl$_3$). This represents the first synthesis of *ent*-Δ^1-tetrahydrocannabinol where absolute stereocontrol in the natural product was not directly linked to the chiral pool.

Synthesis of *ent*-Shikimic Acid (5). The Diels−Alder reaction of acrylimide **2** with furan was also investigated (eq 14). Although 7-oxabicyclo[2.2.1]hept-2-enes are attractive intermediates in organic synthesis,[34] furan is generally held to be a poor diene in Diels−Alder reactions,[35] and only two examples of catalytic asymmetric Diels−Alder reactions with furan or substituted furans have been reported. One study employed α-haloacroleins as the dienophiles,[36] while the other investigated the more reactive 3-(methylthio)furan as the diene component.[7e]

Table 4. The Diels−Alder Reaction of Imide **2** with Furan (eq 14)[a]

(14)

2

[Cu(*tert*-Bu-box)](SbF$_6$)$_2$ **1b**
5 mol%

32

entry	temp	time	conv.[b]	endo/exo[b]	endo ee[c]
1	−20 °C	24 h	98%	10:90	0%
2	−20 °C	2.5 h	88%	66:34	59%
3	−78 °C	42 h	97%	80:20	97%

[a] Reactions were carried out at the indicated temperature in CH$_2$Cl$_2$ with 10 equiv of furan. [b] Conversion and diastereomer ratios were determined NMR spectroscopy. [c] Enantiomeric excess was determined by chiral HPLC. Exo ee <20%.

When the acrylimide-furan reaction (eq 14) was performed under standard screening conditions (5 mol % catalyst **1b**, −20 °C, 24 h), the product was obtained as a 9:1 mixture of exo/endo isomers, both of which were racemic (Table 4, entry 1). However, upon terminating the reaction after only 2.5 h (88%

(29) Reference 23. Attempts to form the diene through the rearrangement of 2-methylbut-3-yn-2-ol with Ag(I) and acetic anhydride resulted in the formation of a mixture of products which were difficult to separate. See: (a) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakley, T. J.; Ullah, Z. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1096−1102. (b) Snider, B. B.; Amin S. G. *Synth. Commun.* **1978**, *8*, 117.

(30) Reactions carried out at 0 °C were not as clean, while reactions at temperatures lower than −20 °C did not exhibit improved diastereoselectivity.

(31) Stoss has provided the precedent for this transformation in the cyclization of the isomeric allylic alcohol: Stoss, P.; Merrath, P. *Synlett* **1991**, 553−554.

(32) (a) Petrzilka, T.; Haefliger, W.; Sikemeier, C. *Helv. Chim. Acta* **1969**, 1102. (b) Archer, R. A.; Johnson, D. W.; Hagaman, E. W.; Moreno, L. N.; Wenkert, E. *J. Org. Chem.* **1977**, *42*, 490−495.

(33) (a) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860−5865. (b) Crombie, L.; Crombie, W. M. L.; Jamieson, S. V.; Palmer, C. J. *J. Chem Soc., Perkin Trans. 1* **1988**, 1243−1250.

(34) For reviews, see: (a) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195−1220. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173−185.

(35) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299−5302.

(36) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979−3982.

conversion), the endo product, formed in 59% ee, was now found to be the predominant product diastereomer (endo/exo, 66:34), (entry 2). These results suggested that at −20 °C, the reaction was reversible. Accordingly, when the reaction was carried out at −78 °C, the endo/exo ratio climbed to 80:20, while the endo isomer was formed in 97% ee (entry 3). A 20 mmol scale reaction yielded enantiomerically pure endo isomer **32** in 67% yield after recrystallization.

To demonstrate the utility of this reaction, we undertook a synthesis of shikimic acid, an intermediate in the plant biosynthesis of aromatic amino acids and quinic acid.[37] Previous syntheses of racemic shikimic acid and related derivatives have originated from Diels−Alder adducts of furan with acrylonitrile[38] and methyl acrylate.[39] On the basis of precedent established in these studies, imide **32** was converted to its derived methyl ester **33** via the intermediate *S*-ethyl thioester [(a) LiSEt;[22] (b) Cs$_2$CO$_3$, MeOH] in 93% overall yield (Scheme 4).[40]

Scheme 4[a]
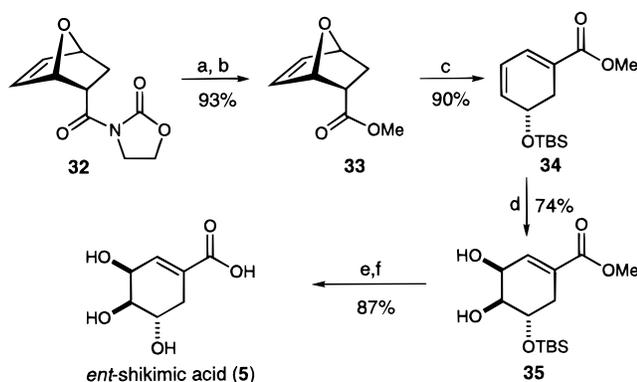
[a] (a) LiSEt, THF, −20 °C; (b) Cs$_2$CO$_3$, MeOH, 0 °C; (c) LiHMDS, THF, −78 to 0 °C, then TBSOTf, 2,6-lutidine, −78 °C; (d) OsO$_4$, NMO, THF, H$_2$O, 0 °C; (e) TBAF, THF; (f) TMSOK, THF, then IR-120, H$_2$O.

LiHMDS-promoted ring opening of **33** resulted in isolation of substantial amounts of methyl benzoate; therefore, a modification of the procedure of Campbell was employed in which the lithium alkoxide was trapped in situ with TBSOTf to provide silyl ether **34** in 90% yield.[40] Dihydroxylation (OsO$_4$, NMO, THF, H$_2$O) of **34** proceeded with good diastereoselectivity (10:1) to deliver diol **35** (74%), which was desilylated (TBAF, THF) in 97% yield to provide *ent*-methyl shikimate. Although the saponification of methyl shikimate is reported to be capricious due to varying amounts of aromatized byproducts,[37] it was found that potassium trimethylsilanolate[41] cleanly afforded *ent*-shikimic acid (**5**) in 90% yield after purification by ion-exchange chromatography (Amberlyst IR-120, H$_2$O).[42] This material

(37) For a brief review of the role of shikimic acid in plant biosynthesis and the syntheses of the shikimates, see Campbell, M. M.; Sainsbury, M.; Searle, P. A. *Synthesis* **1993**, 179−193.

(38) Rajapaksa, D.; Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1984**, *6*, 826−827.

(39) (a) Campbell, M. M.; Kaye, A. D.; Sainsbury, M. *Tetrahedron Lett.* **1983**, *24*, 4745−4746. (b) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron Lett.* **1984**, *25*, 1629−1630. (c) Campbell, M. M.; Kaye, A. D.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 2461−2470. (d) Campbell, M. M.; Sainsbury, M.; Yavarzadeh, R. *Tetrahedron* **1984**, *40*, 5063−5070.

(40) Attempts to open cycloadduct **32** under basic conditions (LiHMDS, TBSCl, or TBSOTf, Et$_3$N) to the derived cyclohexadienol proved unsatisfactory.

(41) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.

(42) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765−1771.

exhibited spectroscopic data comparable to that of a natural sample, with the exception of the rotation, which was opposite in sign [α]^{25}$_D$ −150 (*c* = 0.80, MeOH); [α]^{25}$_D$ (synthetic) +142 (*c* = 0.80, MeOH)]. This synthesis again established that the absolute sense of induction in the Diels−Alder reaction was consistent with the proposed model.[2]

Effect of Diene Substitution on Reaction Selectivity. The unanticipated turnover in diastereoselectivity between the reactions of 1-acetoxybutadiene and 1-acetoxy-3-methylbutadiene may be understood as the result of a steric interaction in the latter case between the 3-methyl group and the ligand in the endo trajectory. A qualitative examination of models of the endo and exo transition states for this reaction (Figure 2) suggests that the 3-substituent, X, encounters nonbonding interactions with the chiral bis(oxazoline) ligand in the endo transition state. It follows that a steric interaction between the ligand and the methyl substituent on the diene in the *endo* transition state could account for the turnover in diastereoselectivity from the corresponding reaction of 1-acetoxybutadiene (vide supra).[43]

Examination of thermal and catalyzed diastereoselectivities provides further evidence for a steric interaction between the 3-methyl group and the catalyst in the endo transition state. The catalyzed reactions of 1-acetoxybutadiene (85:15 endo/exo) were slightly more endo-selective than the thermal reaction (75:25). Other dienes behaved similarly.[44] However, 1-acetoxy-3-methylbutadiene showed a greater exo preference in the catalyzed reaction (73:27 exo/endo) than in the thermal reaction (60:40 endo/exo).
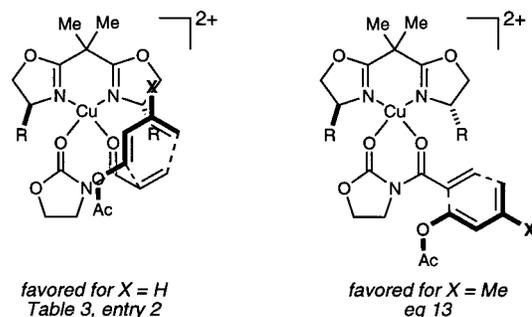

favored for X = H   favored for X = Me
Table 3, entry 2   eq 13

Figure 2. Endo and exo approaches of 1-acetyoxybutadienes to catalyst-bound imide dienophile.

The effect of a 3-methyl substituent on reactions of 1-acetoxybutadienes is anticipated to be general. In particular, this steric effect could explain the anomalously low selectivities obtained in reactions of 2,3-dimethylbutadiene (65% ee) and isoprene (60% ee, Table 2). Both of these dienes are presumed to approach the catalyst-bound imide largely via an exo transition state. If the catalyst is incapable of imparting high selectivities to the exo trajectory, then a lower enantioselectivity would be anticipated (in these cases, endo and exo transition states give rise to the same product).

The question then arises as to why the exo trajectory of 2,3-dimethylbutadiene and isoprene would be unselective while that of 1-acetoxy-3-methylbutadiene is very selective (97% ee). We postulate that the presence of the (1*E*)-substitution provides a steric interaction with the ligand that is missing in the other

(43) An exo-selective Diels−Alder reaction has been designed on the basis of steric interactions between an approaching diene and an imidizolidinonyl carbene dienophile in the endo transition state. See: Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438−6439.

(44) 1-Phenylbutadiene: thermal = 82:18 endo/exo; catalyzed = 85:15 endo/exo. 1-Phenylthiobutadiene: thermal = 65:35 endo/exo; catalyzed = 98:2 endo/exo. 1-Benzyloxycarbonylaminobutadiene: thermal = 49:51 endo/exo; catalyzed = 72:28 endo/exo.
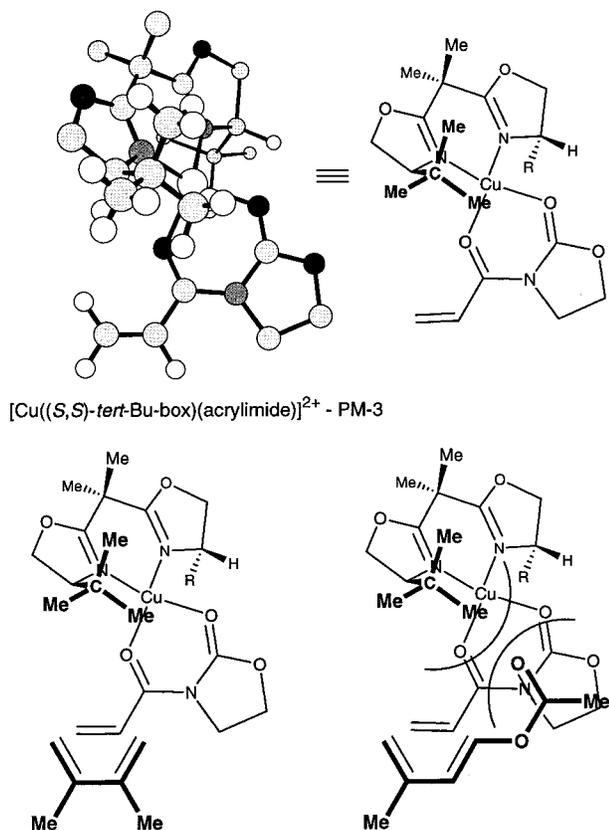
[Cu((*S,S*)-*tert*-Bu-box)(acrylimide)]$^{2+}$ - PM-3

Figure 3. Minor exo approaches of 2,3-dimethylbutadiene and of 1-acetoxy-3-methylbutadiene to [Cu((*S,S*)*tert*-Bu-box)(imide)].

two cases. As shown in Figure 3, the disfavored exo approach of 2,3-dimethylbutadiene to the catalyst-bound imide does not encounter substantial steric interaction with the ligand. However, 1-acetoxy-3-methylbutadiene does contact the ligand substituent in the disfavored exo approach.

If the preceding analysis is correct, then one would anticipate the exo enantioselectivities of (1*E*)-substituted dienes to be high, while the exo selectivities of (1*Z*)-substituted dienes should be lower. In fact, these expectations are borne out. The trans products of the reactions of 1-acetoxybutadiene (90% ee), 1-phenylthiobutadiene (89% ee), and 1-(benzyloxycarbonylamino)butadiene (97% ee) were formed with high enantioselectivity (Table 3).[45] However, the exo products of cyclohexadiene (29–53% ee) and furan (<20% ee, Table 4) were generated relatively unselectively.

(A) Intramolecular Diels–Alder Reactions. Prior to this investigation, only a handful of studies had been reported which described catalytic asymmetric intramolecular Diels–Alder (IMDA) reactions.[8,9e,10] Of these, only one catalytic system has been reported to effect the enantioselective IMDA reaction of unsaturated trienimides such as **36**.[8] Our interest in this class of reactions extends back some years, having reported previously that chiral trienimides undergo highly diastereoselective IMDA reactions when mediated by dimethylaluminum chloride.[20] We speculated that complexes **1a** and **1b** would possess sufficient Lewis acidity and facial discrimination to effect an enantioselective version of this cycloaddition reaction.

The synthesis of the requisite trienimides is outlined in Scheme 5. Trienimide **36**, possessing a three-carbon tether between the diene and dienophile, was prepared from nitrile

Scheme 5^a
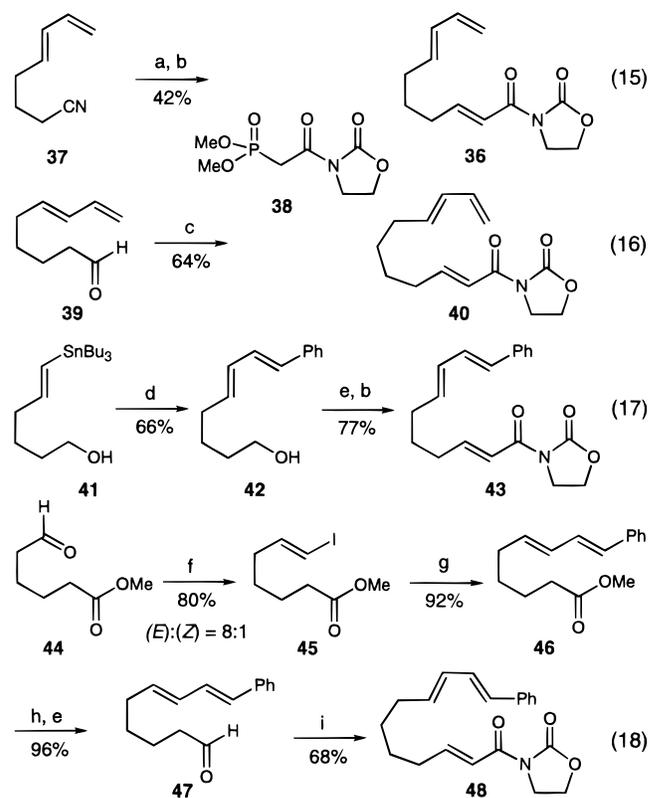
^{a} (a) DIBAL, Et$_2$O, 0 °C; 1 M HCl; (b) **38**, NaHMDS, THF, 0 °C to 25 °C; (c) **38**, Et$_3$N, LiCl, CH$_3$CN, 25 °C; (d) (*E*)-*β*-styryliodide, (PhCN)$_2$PdCl$_2$ (3 mol %), DMF, 25 °C; (e) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, −78 °C; Et$_3$N, to 0 °C; (f) CrCl$_2$, CHI$_3$, dioxane/THF (6:1), 25 °C; (g) (*E*)-*β*-styryltributyltin, (PhCN)$_2$PdCl$_2$ (3 mol %), DMF, 25 °C; (h) DIBAL, CH$_2$Cl$_2$, 0 °C; (i) **38**, (*i*-Pr)$_2$NEt, LiCl, CH$_3$CN, 25 °C.

37 (eq 15), whose synthesis has been described by Roush.[46] Reduction of **37**, followed by Horner-Emmons homologation with phosphonate reagent **38**, itself prepared via an Arbuzov reaction of 2-(bromoacetyl)-3-oxazolidinone and trimethyl phosphite, provided **36**. The higher homologue **40** was prepared via a similar olefination of aldehyde **39** (eq 16).[47] Trienimide **43**, the phenyl-substituted variant of **36**, was synthesized via the following sequence: Pd(0)-catalyzed coupling of vinylstannane **41**[48] and (*E*)-iodostyrene to afford dienic alcohol **42**, oxidation under Swern conditions,[49] and immediate homologation with phosphonate **38** (eq 17). The higher homologue **48** was accessed beginning with Takai olefination[50,51] of aldehyde ester **44**[52] to give vinyl iodide **45**, which underwent Pd(0)-catalyzed coupling with (*E*)-*β*-tributylstannylstyrene to afford dienic ester **46**. Reduction with DIBAL, oxidation, and Horner-Emmons homologation led to the desired trienimide **48** (eq 18).

(46) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269−2283.

(47) We have prepared **39** on a small scale (<1 g) via Pd(0) coupling of vinyltributylstannane with iodide **45**, followed by DIBAL reduction and Swern oxidation in analogy to the preparation on **47**. This route is probably not amenable to large-scale preparation. For an alternate preparation, see Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200−5211.

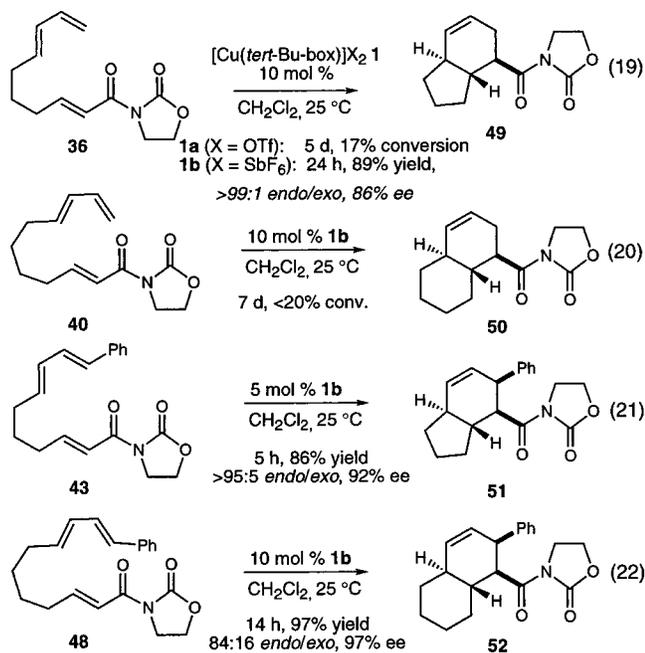(48) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883−2894.

(49) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(50) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(51) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.

(52) Claus, R. E.; Schreiber, S. L. *Organic Syntheses, Collective Volume VII*; Freeman, J. P., Ed.; Wiley: New York, 1990; p 168−171.

(45) It was not possible to accurately assay the enantioselectivity of the trans product of 1-phenylbutadiene reactions, due to epimerization during the thiolate cleavage reaction.

Scheme 6

Our initial studies focused on the reaction of **36** with the triflate complex **1a** (Scheme 6, eq 19). After 5 days at room temperature (10 mol % **1a**, CH$_2$Cl$_2$), only 17% conversion to cycloadduct **49** was observed (^{1}H NMR spectroscopy); however, by employing SbF$_6$ catalyst **1b** (10 mol %, 25 °C, CH$_2$Cl$_2$), we isolated the desired cycloadduct as a single diastereomer in 89% yield and 86% ee after 24 h. The relative and absolute configuration of this adduct was established by transformation to the known benzyl ester ($[\alpha]^{25}_D$ −23.8 (c = 0.90, CHCl$_3$)) whose absolute configuration had been previously established.[20] By way of comparison, the optimal conditions for the chiral oxazolidinone-derived triene variant of **36**, promoted by dimethylaluminum chloride, afforded a 97:3 mixture of endo isomers (endo/exo, >99:1) in 65% yield.[20] The similar endo face selectivities observed between the enantioselective and diastereoselective reactions render these two processes quite competitive.

On the basis of our results with trienimide **36**, we were disappointed to find that the higher homologue **40** failed to undergo cycloaddition with SbF$_6$ catalyst **1b** to a significant degree after extended reaction times (>1 week) (eq 20). This was especially surprising in light of the facility with which chiral variants of **40** undergo cycloaddition.[20] The reason for this anomolous behavior has not been identified.

The illustrated phenyl-substituted dienes **43** and **48** uniformly afforded better reactivity and enantioselectivity than their unsubstituted counterparts **36** and **40** in the IMDA process. Upon treatment of trienimide **43** with 5 mol % of catalyst **1b**, under the usual reaction conditions (CH$_2$Cl$_2$, rt), cyclization to the desired adduct **51** was observed after only 5 h with complete diastereoselectivity in 86% yield and 92% ee (eq 21). The higher homologue **48** was transformed in 97% yield (10 mol % **1b**) to the corresponding cycloadduct **52** as a mixture of diastereomers (endo/exo = 84:16), with the endo isomer delivered in 97% ee and the exo in >95% ee (eq 22). From these results, it may be deduced that a longer diene tether allows greater conformational flexibility, eroding reaction diastereoselectivity. As expected, the phenyl group enhanced diene reactivity, manifested in the divergent outcomes using unsubstituted **40** versus phenyl-substituted **48**. The relative stereochemistry of each cycloadduct

was deduced by appropriate NOE experiments; the structure of **51** was confirmed by X-ray analysis. The absolute stereochemical assignments of **51** and **52** were made by analogy to **49**.

(B) Synthesis of (−)-Isopulo'upone (6). A synthesis of (−)-isopulo'upone (**6**), isolated in 1993 from mollusks *Navarax inermis* and *Bulla Gouldiana*, provided an interesting test of substrate complexity for the IMDA process.[53] Preparation of the cyclization substrate was initiated by the Pd(0)-catalyzed coupling of vinyl iodide **53** with vinylstannane **41** to afford the desymmetrized (*E*,*E*)-diene **54** (Scheme 7).[54] Swern oxidation of **54** afforded an aldehyde that was immediately treated with phosphonate **38** (NaHMDS, THF) to afford trienimide **55** in 77% yield (2 steps) as a separable 27:1 mixture of (*E*) and (*Z*) isomers.

With the requisite trienimide **55** in hand, cycloaddition to the desired adduct **56** was achieved with 5 mol % of the SbF$_6$ catalyst **1b** (24 h, 25 °C) in 81% yield. The cycloaddition proceeded with high diastereo- and enantioselectivity (>99:1 endo/exo, 96% ee), delivering the isopulo'upone skeleton with all four contiguous stereogenic centers established in the correct relative and absolute configuration (vide infra). Imide **56** was transformed to its derived thioester **57** in 91% yield by treatment with LiSEt (THF, 0 °C, 15 min).[22] Reduction of the thioester to aldehyde **58** using Pd(0)/triethylsilane[55] was plagued by concomitant saturation of the olefin; however, a modification in which Lindlar's catalyst was employed[52] in the presence of an excess of a "sacrificial" olefin, 1-decene, allowed the transformation to be conducted without detectable alkene reduction, cleanly affording **58** without the need of purification. Treatment of this aldehyde with methylmagnesium chloride (THF, −78 °C) and subsequent silyl ether deprotection (1% HCl/EtOH, 10 min, 25 °C) afforded diol **59** in 90% yield (3 steps) as an 8:1 mixture of diastereomers at the newly formed hydroxyl stereocenter. An X-ray crystal structure of **59** confirmed the relative stereochemical assignments made previously.[11c] While inconsequential to the study at hand, the major product observed in this addition reaction is consistent with the diastereomer predicted by the Felkin-Ahn model.[56] The diastereomeric mixture of diols **59** was oxidized to a single keto aldehyde **60** (83%), then treated with the ylide derived from tributylphosphonium salt **61** to afford (−)-isopulo'upone (**6**) with excellent chemo- and stereoselectivity (*E*/*Z* = 12:1) and yield (90%).[57] The spectral data (^{1}H, ^{13}C, IR, HRMS) for **6** matched those reported for the natural product, while the absolute stereochemical assignment of the Diels−Alder reaction was confirmed by the specific rotation: $[\alpha]^{25}_D$ (synthetic) −143 (c = 0.38, hexane); $[\alpha]^{25}_D$ (lit.) −119 (c = 0.40, hexane).[53a] Thus, the sense

(53) (a) Spinella, A.; Alvarez, L. A.; Cimino, G. *Tetrahedron* **1993**, *49*, 3203−3210. (b) A racemic synthesis of isopulo'upone has appeared: Matikainen, J.; Kaltia, S.; Hase, T. *Synth. Commun.* **1995**, *25*, 195−201. (c) Racemic and auxiliary-mediated asymmetric syntheses of pulo'upone (exocyclic double bond out of conjugation) have appeared: (i) Burke, S. D.; Piscopio, A. D.; Buchanan, J. L. *Tetrahedron Lett.* **1988**, *29*, 2757−2960. (ii) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 5885−5888. (iii) Sugahara, T.; Iwata, T.; Yamaoka, M.; Takano, S. *Tetrahedron Lett.* **1989**, *30*, 1821−1824.

(54) Synthesis of **53** and **41** from 5-hexyn-1-ol: (a) TBSCl, Et$_3$N, DMAP (cat.), CH$_2$Cl$_2$, rt, 1.5 h (86%); (b) (i) Cp$_2$ZrH(Cl), toluene, rt, 12 h; (ii) N-iodosuccinimide, rt, 18 h (88%); (c) (i) *n*-BuLi, THF, −78 °C; Bu$_3$SnCl; (ii) TBAF, THF, rt, 12 h (61%). See ref 48.

(55) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

(56) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(57) Earlier attempts to execute this reaction with the analogous phosphonate-derived reagent 2-pyr-CH(M)P(O)(OMe)$_2$ (M = Li, Na, K) led to proton transfer-induced intramolecular aldol addition of **60**.

Scheme 7[a]
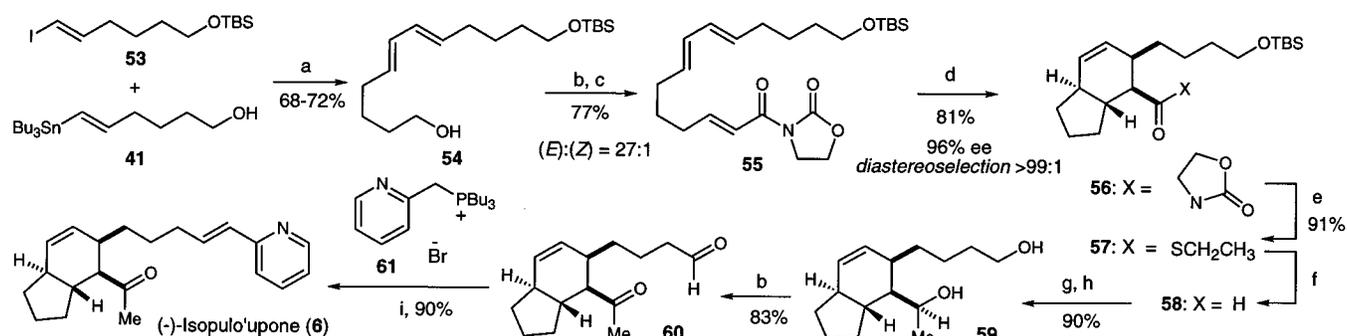
[a] (a) Four mole percent $Pd_2(dba)_3 \cdot CHCl_3$, DMF, rt, 16 h; (b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; Et_3N, to −40 °C; (c) **38**, NaHMDS, THF, rt, 26 h; (d) 5 mol % **1b**, CH_2Cl_2, rt, 24 h; (e) LiSEt, THF, 0 °C, 15 min; (f) Et_3SiH, 5% $Pd/CaCO_3/PbO/quinoline$, 1-decene, acetone, rt, 2 h; (g) MeMgCl, THF, −78 °C; (h) 1% HCl/EtOH, rt, 10 min; (i) **61**, *n*-BuLi, THF, −20 °C, then **60** rt, 45 min.

of induction that all catalyzed trienimide IMDA reactions reported in this study is consistent with our proposed model (Figure 1).[6]

It is noteworthy that the enantioselectivity of observed for the key step (**55** → **56**) in this synthesis (96%) is significantly greater than that observed for the analogous reaction lacking alkyl substitution on the diene terminus (Scheme 7, eq 19, 86% ee). We thus conclude that this family of cationic Cu(2+) catalysts should also be effective for similarly substituted enantioselective IMDA processes.

[Cu((*S,S*)-pybox)](SbF$_6$)$_2$ Catalyzed Cycloadditions. In conjunction with the development of [Cu(*t*-Bu-box)](X)$_2$ complexes as chelating chiral Lewis acids, the evaluation of related square planar Cu(2+) complexes derived from bis(oxazolinyl)-pyridine (pybox) ligands was also undertaken.[58] In the absence of counterion involvement, the cationic trigonal planar complexes **8** and **9** would be expected to bind Lewis bases in the ligand plane, creating a sterically differentiated environment for the two π-surfaces of a coordinated dienophile (eq 23).


(23)
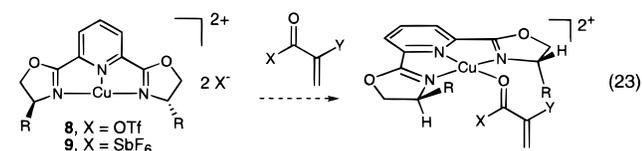
(A) Catalyst Preparation. Solutions of the (*S,S*)-pybox ligands **7a−7c** in CH_2Cl_2 were complexed with $Cu(OTf)_2$ to form blue solutions of the chiral triflate complexes **8a−8c** (eq 24).

(24)

a: R = CMe$_3$; b: R = CHMe$_2$; c: R = Ph

(25)

a: R = CMe$_3$; b: R = CHMe$_2$; c: R = Ph; d: R = Bn
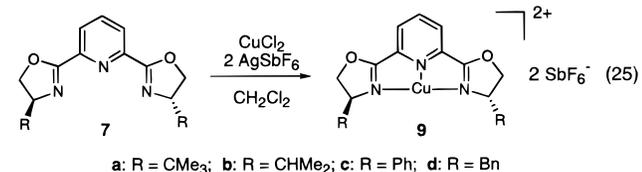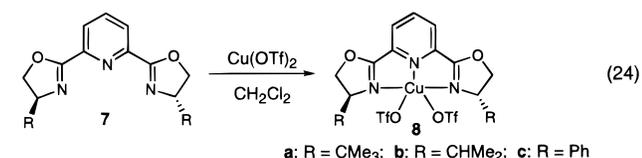
The analogous SbF$_6$ complexes were also prepared through complexation of the pybox ligand with $CuCl_2$ and 2 equiv of

$AgSbF_6$ in CH_2Cl_2 for several hours at room temperature (eq 25). The resulting AgCl precipitate was removed by filtration through a plug of cotton in air to provide blue or green catalyst solutions of **9a−9d**.

Structural studies were undertaken on both the triflate and SbF$_6$ complexes **8b** and **9b** as their derived crystalline hydrates (**62** and **63**) to determine the nature of both metal center architecture and counterion involvement (eqs 26, 27).[6]

(26)

(27)
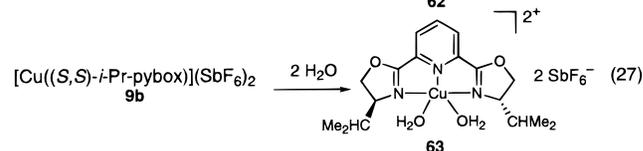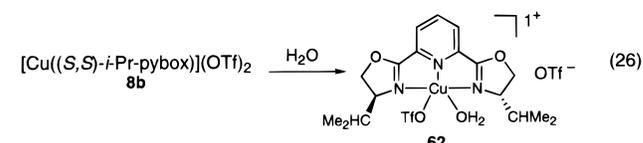
The impact of counterion on the aquo complexes is documented in the X-ray structures of **62** and **63**[3a] provided in Figure 4. The X-ray structure of **62** clearly substantiates that the triflate counterions are associated with the metal center to varying degrees (Cu−OTf = 2.359 and 2.489 Å). On the other hand, the structure of the bis(aquo) SbF$_6$ complex **63** adopts the expected square pyramidal geometry with the more tightly bound water located in the equatorial plane (Cu−OH$_2$ = 1.985 Å) and the second bound water more loosely coordinated in the apical position (Cu−OH$_2$ = 2.179 Å). Both of these structures support the premise that the coordination of a carbonyl Lewis base to either complex would be expected to occur in the more Lewis basic site in the ligand plane as previously projected (eq 23).

(B) Acrolein Dienophiles. [Cu(pybox)](OTf)$_2$ complexes **8a−c** serve as chiral Lewis acids in the reactions of methacrolein[9,59] with cyclopentadiene (Table 5, eq 28). With 5 mol % of the *tert*-butyl pybox catalyst **8a**, exo cycloadduct **64** (X = Me, 96:4) was obtained in 85% ee (entry 1); however, extended reaction times (116 h) were required for complete conversion. The isopropyl pybox catalyst **8b** provided lower selectivity (entry 2), and a reversal in absolute sense of induction was observed with the phenyl-substituted ligand (entry 3). This latter result suggests the existence of a possible substituent-related

(58) Four-coordinate Cu(II) complexes exhibit a strong tendency toward square planar geometries. See: Hathaway, B. J. in *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York; 1987; Vol. 5, Chapter 53.

(59) (a) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814−3815. (b) Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966−8967. (c) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437−438.
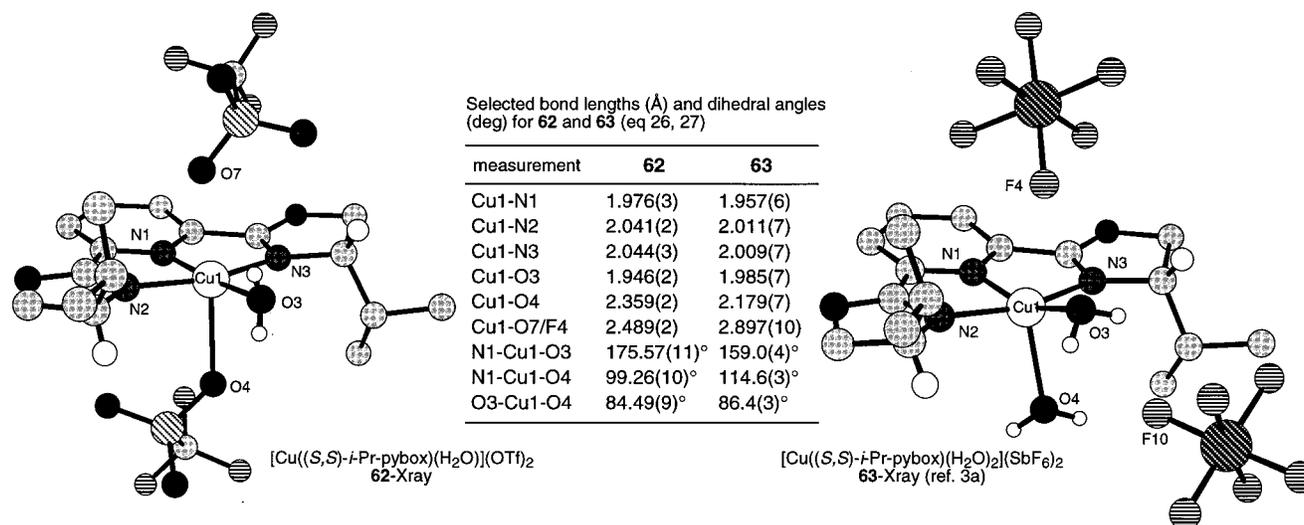
Selected bond lengths (Å) and dihedral angles (deg) for **62** and **63** (eq 26, 27)

measurement	62	63
Cu1–N1	1.976(3)	1.957(6)
Cu1–N2	2.041(2)	2.011(7)
Cu1–N3	2.044(3)	2.009(7)
Cu1–O3	1.946(2)	1.985(7)
Cu1–O4	2.359(2)	2.179(7)
Cu1–O7/F4	2.489(2)	2.897(10)
N1–Cu1–O3	175.57(11)°	159.0(4)°
N1–Cu1–O4	99.26(10)°	114.6(3)°
O3–Cu1–O4	84.49(9)°	86.4(3)°

$[Cu((S,S)\text{-}i\text{-Pr-pybox})(H_2O)](OTf)_2$
62-Xray

$[Cu((S,S)\text{-}i\text{-Pr-pybox})(H_2O)_2](SbF_6)_2$
63-Xray (ref. 3a)

Figure 4. Crystallographic structures of the $[Cu((S,S)\text{-}i\text{-Pr-pybox})](H_2O)_n]X_2$ complexes **62** and **63** along with selected bond lengths and angles.

Table 5. Reaction of 2-Substituted Acrolein Derivatives with Cyclopentadiene Catalyzed by $[Cu((S,S)\text{-R-pybox})](X)_2$ (eq 28)[a]
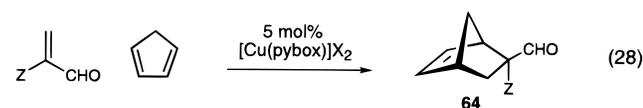
catalyst	dienophile (temp)	time[b]	exo/endo[c]	exo ee[d]
8a (R = CMe₃)	Z = Me (−20 °C)	116 h	97:3	85% (S)
8b (R = CHMe₂)	Z = Me (−20 °C)	23 h	96:4	52% (S)
8c (R = Ph)	Z = Me (−20 °C)	80 h	94:6	39% (R)
8a (R = CMe₃)	Z = Br (−20 °C)	12 h	96:4	78% (R)
8a (R = CMe₃)	Z = Br (−40 °C)	60 h	97:3	87% (R)
9a (R = CMe₃)	Z = Me (−40 °C)	8 h	97:3	92% (S)
9b (R = CHMe₂)	Z = Me (−40 °C)	6 h	96:4	72% (S)
9c (R = Ph)	Z = Me (−40 °C)	6 h	96:4	49% (R)
9d (R = Bn)	Z = Me (−40 °C)	6 h	96:4	90% (S)
9a (R = CMe₃)	Z = Br (−78 °C)	12 h	98:2	96% (R)
9d (R = Bn)	Z = Br (−78 °C)	12 h	98:2	95% (R)

[a] Reactions were carried out in CH_2Cl_2 with 5 equiv of diene. [b] Time required for >95% conversion. [c] The diastereomer ratio was determined by GLC analysis. [d] Enantiomeric excesses were determined as follows: methacrolein: GLC analysis after conversion to the acetal of (−)-(2R,4R)-pentanediol; 2-bromoacrolein, GLC analysis after conversion to the dimethyl acetal.

electronic effect imparted to the reaction by the aryl moiety. The *tert*-butyl catalyst **8a** was also employed in the reaction of cyclopentadiene with the more reactive 2-bromoacrolein (entries 4 and 5). At −40 °C, the exo cycloadduct **64** (X = Br) was formed with enantioselectivities as high as 87%. The absolute sense of induction (as shown) in each instance was determined by comparison of rotations to literature values.[60]

While these data indicated that the pybox-Cu(II) complexes afforded the architecture necessary for asymmetric induction, the long reaction times severely limit practical applications of this system. Although the triflate counterion had been chosen on the assumption that the $[Cu(pybox)](OTf)_2$ complex would dissociate upon substrate binding, this postulate was tested through the evaluation of the less coordinating counterions BF_4, PF_6, and SbF_6. From this screen, the SbF_6 catalysts **9** (eq 25) were found to provide optimal reactivity, without sacrificing reaction enantioselectivity. For example, the *tert*-butyl-substituted complex **9a** proved to be optimal, affording 92% ee in

(60) Methacrolein/cyclopentadiene adduct: ref 9c. 2-Bromoacrolein/cyclopentadiene adduct: (c) ref 59b.

the reaction of methacrolein at −40 °C (Table 5, entry 6). The benzyl catalyst **9d** was comparable to the *tert*-butyl derivative, providing the cycloadduct in 90% ee (entry 9). This phenyl-alanine-derived ligand is an attractive alternative to the more expensive *tert*-leucine variant. Similar trends were observed with 2-bromoacrolein: the best result was provided by *tert*-butyl catalyst **9a** (96% ee, entry 10), although the benzyl ligand afforded comparable enantioselection (95% ee, entry 11).

The preceding data document the importance of counterion selection in achieving a sufficiently reactive metal center to deliver a practical level of catalytic activity. The qualitative kinetic data for these two catalysts (Table 5) is also consistent with the X-ray structure of the triflate aquo complex **62** shown in Figure 2 that illustrates the fact the triflate counterions associate with the metal center. Accordingly, we speculate that the Lewis acidity of the triflate-based catalysts **8** is being buffered by the triflate counterion. In conclusion, these data support the conclusion that the SbF_6 complexes **9** are comparable to other catalysts reported in the literature for this family of reactions.[9,59]

(C) Acrylate Dienophiles. This class of dienophiles has been studied under the influence of both stoichiometric[61] and catalytic[62] conditions with metalloid chiral Lewis acid catalysts. They were also evaluated in the Diels–Alder reaction with cyclopentadiene with the chiral pybox complexes $[Cu((S,S)\text{-pybox})](SbF_6)_2$ **9a**–**9d** (Table 6, eq 29). This reaction was stereoregular, producing the same enantiomer (R) regardless of the pybox or ester substituent. *tert*-Butyl acrylate (R′ = CMe₃) proved to be the optimal substrate (entries 1–4). A survey of the ligands revealed that benzyl pybox catalyst **9d** provided the best selectivity (92% ee, entry 4), while the others (**9a**–**c**) provided selectivities in the range of 83–88% ee (entries 1–3). Methyl acrylate and phenyl acrylate underwent cycloadditions with lower selectivities (entries 5 and 6, respectively). The absolute stereochemistry was determined by reduction of the esters to the corresponding alcohols and comparison of optical rotation to literature values.[63]

(61) (a) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954−974. (b) Devine, P.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396−399.
(62) (a) Hawkins, J. M.; Loren, S. J.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657−1660. (b) Maruoka, K.; Conception, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501−3503.
(63) Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Warnhoff, P. R.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986.

Table 6. Reaction of Acrylate Esters with Cyclopentadiene Catalyzed by [Cu((S,S)-R-pybox)](SbF$_6$)$_2$ **9** (eq 29)^a
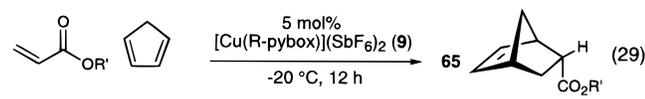
| entry	catalyst	ester	endo/exo^b	endo ee^b
1	**9a** (R = CMe$_3$)	R′ = CMe$_3$	96:4	84%
2	**9b** (R = CHMe$_2$)	R′ = CMe$_3$	98:2	88%
3	**9c** (R = Ph)	R′ = CMe$_3$	96:4	83%
4	**9d** (R = Bn)	R′ = CMe$_3$	98:2	92%
5	**9d** (R = Bn)	R′ = Me	95:5	85%
6	**9d** (R = Bn)	R′ = Ph	92:8	44%

^{a} Reactions were carried out in CH$_2$Cl$_2$ with 5 equiv of diene. ^{b} Diastereomer ratios and enantiomeric excesses were determined by chiral GLC.

(D) Models for Diels−Alder Reactions of Monodentate Dienophiles. Simple models that correlate catalyst-dienophile structure with dienophile face selectivity are provided below (eq 30, 31). On the basis of the crystal geometry of the [Cu-((S,S)-i-Pr-pybox)(H$_2$O)$_2$](SbF$_6$)$_2$ complex (**63**) (Figure 2), it is presumed that aldehyde dienophiles coordinate to the copper center in a square planar geometry. The principal uncertainty in the prediction of the stereochemical outcome of the reaction is associated with the reacting dienophile conformation which presents options for cycloaddition out of either the *s*-cis or *s*-trans conformation. The relative reactivity of *s*-cis and *s*-trans acrolein[64] complexes has been addressed at the ab initio level by Houk and co-workers, who find that the lower LUMO energies of the *s*-cis conformer favor reaction out of this less stable conformer[65] through both the exo and endo transition states.[66] This projection, when integrated into the proposed model for the reactive conformation of the coordinated dienophile (**66**), leads to a clear prediction for the stereochemical course of the exo- (eq 30) and endo-selective (eq 31) Diels−Alder reactions with cyclopentadiene. Our experimental results on the exo-selective reactions with methacrolein and bromoacrolein (Table 5) and the endo-selective cycloaddition with acrolein (eq 32) are consistent with this model.
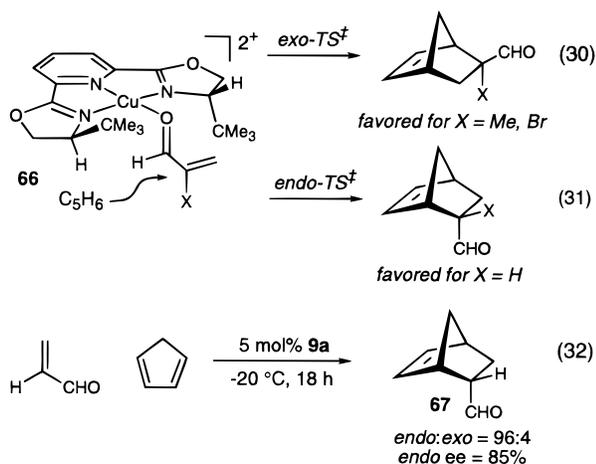
The construction of a model for the acrylate−catalyst complex has been aided by the ab initio-based force field modeling of the transition states of these reactions by Houk and co-workers.[67] This study concludes that the reacting geometry for this metal-complexed dienophile is *s*-trans with the metal complexed to the oxygen lone pair syn to the double bond as depicted below (eqs 33, 34). This is also the observed geometry of the Hawkins

alkyldichoroborane-methyl crotonate complex.[61a] Unfortunately, qualitative analysis of the nonbonding interactions in catalyst−acrylate complex **68** leads to the wrong stereochemical prediction for the course of the cycloaddition (eq 33). An alternative model that is consistent with the stereochemical outcome of the reaction follows from the less symmetrical complex **69** (eq 34). As illustrated, the *Si*-enantioface of the dienophile may be exposed through rotation of the complexed acrylate about the Cu−O bond.
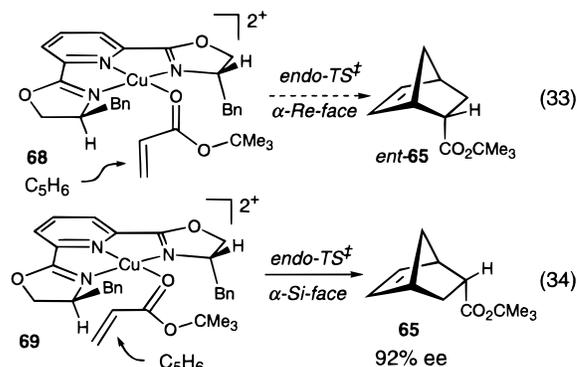
Conclusion

Although a number of chiral metal catalysts have been described which are capable of promoting Diels−Alder reactions of cyclopentadiene, the results in this report demonstrate that bis(oxazoline) copper complexes, particularly hexafluoroantimonate complex [Cu((S,S)-t-Bu-box)](SbF$_6$)$_2$ (**1b**), are highly effective at promoting reactions of acyloxazolidinone-derived dienophiles with less reactive dienes. With this catalyst, a wide range of cyclic and linear dienes react with imide **2** in greater than 90% ee. The application of this catalyst to intramolecular cycloadditions has also proven to be possible. The power of the Diels−Alder reaction lies in its ability to assemble ring systems and multiple contiguous stereocenters quickly. Due to the reactivity of catalyst **1b** and the high degree of asymmetric induction which it imparts, the complex product cycloadducts that are now available have been utilized in efficient syntheses of *ent*-Δ^1-tetrahydrocannabinol (**4**), *ent*-shikimic acid (**5**), and isopulo′upone (**6**).

We have also extended the scope of the copper-catalyzed Diels−Alder reaction to include monodentate dienophiles. The SbF$_6$ pybox catalysts [Cu((S,S)-t-Bu-pybox)](SbF$_6$)$_2$ (**9a**) and [Cu((S,S)-Bn-pybox)](SbF$_6$)$_2$ (**9d**) have been found to catalyze the Diels−Alder reactions of acrolein and acrylate dienophiles with high enantioselectivities.

The observations made in the study of the Diels−Alder reaction, especially the efficacy of chelating dienophiles, have provided the foundation for new enantioselective Cu(II)-

(64) X-ray structures for the following aldehyde complexes have been reported: (a) Methacrolein/BF$_3$ complex: Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. D. *Tetrahedron Lett.* **1992**, *33*, 6945−6948. (b) 2-Heptenal/SnCl$_4$ complex: Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133−3139. (c) Methacrolein/RuL$_n$ complex: Carmona, D.; Cativiela, C.; Elipe, S.; Lahoz, F. J.; Lamata, M. P.; Pilar, M.; de Viu, L. R.; Oro, L. A.; Vega, C.; Viguri, F. *Chem. Commun.* **1997**, 2351−2352. (d) Methacrolein/RuL$_n$ complex: Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1220−1222.

(65) Such a Curtin-Hammett scenario has been proposed for a catalyzed Diels−Alder reaction between 2-bromoacrolein and cyclopentadiene. Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290−8292.

(66) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127−4133.

(67) de Pascual-Teresa, B.; Gonzalez, J.; Asensio, A.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 4347−4356.
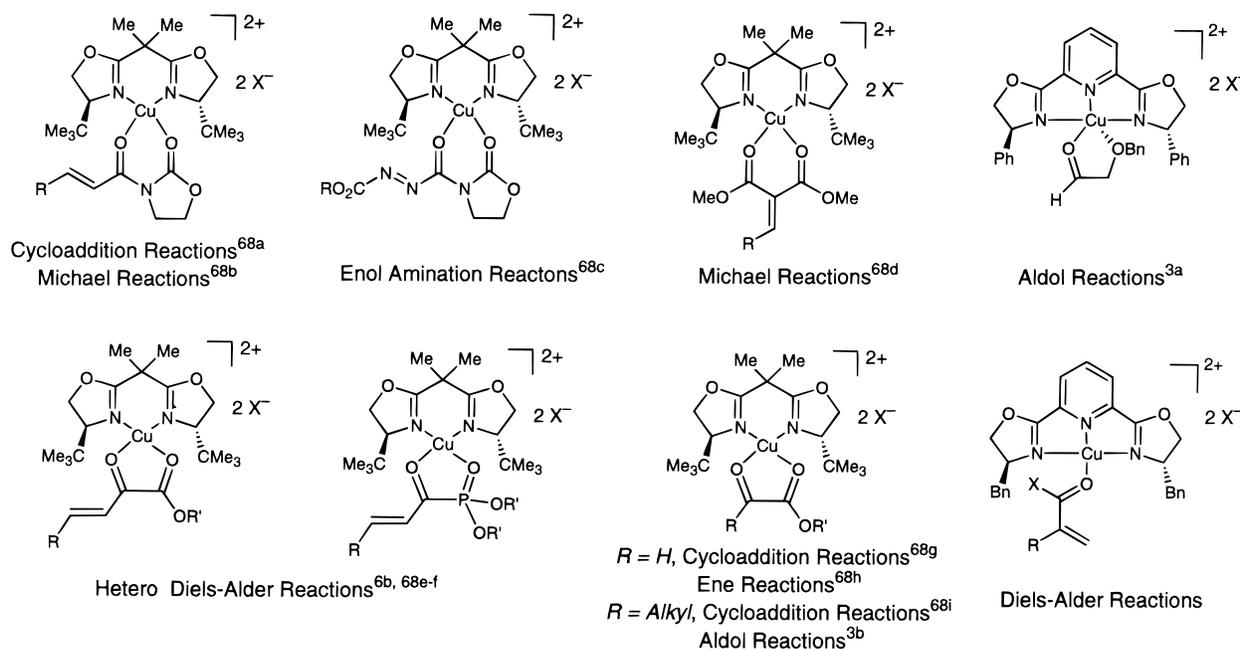
Figure 5. Representative Cu(box) and Cu(pybox) catalyst−substrate complexes implicated in enantioselective reactions.

catalyzed reactions. The requirement of substrate chelation has not hindered these endeavors. As evidenced by Figure 5, reactions catalyzed by bis(oxazoline) Cu(II) complexes span a broad range of important enantioselective bond constructions and have yielded many chiral synthons useful to organic chemists.[68]

Supporting Information Available: Experimental procedures and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JA991191C

(68) (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617−2618. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, in press. (c) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, in press. (d) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995. (e) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. (f) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2404−2406. (g) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117−1122. (h) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824−5825. (i) Yao, S. L.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605.