Enantioselective Synthesis of Dihydropyrans. Catalysis of Hetero Diels−Alder Reactions by Bis(oxazoline) Copper(II) Complexes

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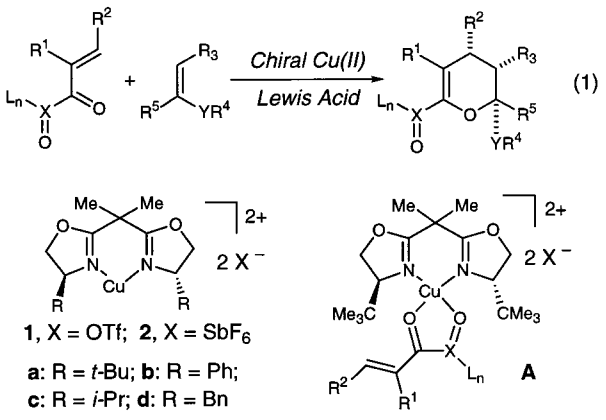
Abstract: C_2-symmetric bis(oxazoline)−Cu(II) complexes **1** and **2** catalyze the inverse electron demand hetero Diels−Alder reaction of α,β-unsaturated carbonyl compounds (heterodiene) with electron-rich olefins (heterodienophile) in high diastereo- and enantioselectivity. α,β-Unsaturated acyl phosphonates and β,γ-unsaturated α-keto esters and amides are effective heterodienes, while enol ethers and sulfides function as heterodienophiles. A range of substitution patterns is possible on the heterodiene: terminal alkyl, aryl, alkoxy, and thioether substituents are all tolerated. The enantioselective synthesis of dihydropyrans by this method has been shown to be straightforward: cycloadditions may be conducted with as little as 0.2 mol % of the chiral catalyst and are readily run on multigram scale. The reactions exhibit a favorable temperature−enantioselectivity profile, with selectivities exceeding 90% even at room temperature. A simple reaction protocol that employs a solid air-stable catalyst, convenient reaction temperatures, and low catalyst loadings is described. The utility of the derived cycloadducts in the preparation of chiral building blocks is demonstrated. Models for asymmetric induction are discussed considering product stereochemistry, X-ray crystallographic data for the solid catalysts, and mechanistic studies.

Introduction

The hetero Diels−Alder reaction of electron-rich alkenes with α,β-unsaturated carbonyl compounds is a powerful method for the preparation of dihydropyrans (eq 1).[2] These cycloadducts,



and their derived tetrahydropyrans, are prevalent structural subunits in numerous important natural products.[3] This article describes the application of chelating Cu(II) chiral Lewis acid complexes **1** and **2** to this hetero-cycloaddition process. The underlying premise for this study was that good levels of asymmetric induction might be anticipated in this process through the intervention of the illustrated catalyst−substrate complex **A**.

Important advances have been made in auxiliary-controlled inverse electron demand hetero Diels−Alder reactions. Tietze has shown that 1-oxa-1,3-butadienes bearing a chiral acyl oxazolidinone moiety participate in highly diastereoselective Lewis acid promoted hetero Diels−Alder reactions with enol ethers (eqs 2 and 3).[4] A noteworthy feature of the work is a reversal in diastereofacial bias modulated by judicious selection of Lewis acid (chelating or nonchelating), enabling the selective formation of either endo diastereoisomer from the same chiral auxiliary. Dujardin demonstrated in complementary work that the heterodienophile may also control the absolute stereochemical course of reaction.[5] Enol ethers derived from mandelic acid react with achiral heterodienes under the influence of catalytic amounts of $Eu(fod)_3$ to give dihydropyrans of high diastereomeric excess (eq 4).[6]

When the present investigation was initiated, one example of a catalytic, enantioselective intermolecular inverse electron demand hetero Diels−Alder reaction had been reported in the literature.[7] Wada and co-workers demonstrated that titanium−TADDOL catalyst **B** may be employed in cycloadditions of

(1) National Science Foundation Predoctoral Fellow.

(2) (a) Tietze, L. F.; Kettschau, G.; Gewart, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.

(3) Representative examples: (a) Monensin: Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737. (b) X-537A (Lasalocid A): Westley, J. W.; Evans, R. H.; Williams, T.; Stempel, A. *Chem. Commun.* **1970**, 71. (c) Bryostatin 1.; Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6846. (d) Miyakolide: Higa, T.; Tanaka, J.; Komesu, M.; Gravalos, D. C.; Puentes, J. L. F.; Bernardinelli, G.; Jefford, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 7587. (e) Zincophorin: Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. K. *J. Antibiot.* **1984**, *37*, 1501. (f) Altohyrtin: Kobayashi, M.; Aoki, S.; Kitigawa, I. *Tetrahedron Lett.* **1994**, *35*, 1243. (g) Phorboxazole: Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (h) Palytoxin: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369.

(4) (a) Tietze, L. F.; Schneider, C.; Grote, A. *Chem. Eur. J.* **1996**, *2*, 139. (b) Tietze, L. F.; Schulz, G. *Liebigs Ann.* **1995**, 1921. (c) Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 980. (d) Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett* **1994**, 509. (e) Tietze, L. F.; Schneider, C. *Synlett* **1992**, 755.

(5) (a) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763. (b) Dujardin, G.; Rossignol, S.; Molato, S.; Brown, E. *Tetrahedron* **1994**, *50*, 9037. (c) Dujardin, G.; Molato, S.; Brown, E. *Tetrahedron: Asymmetry* **1993**, *4*, 193.

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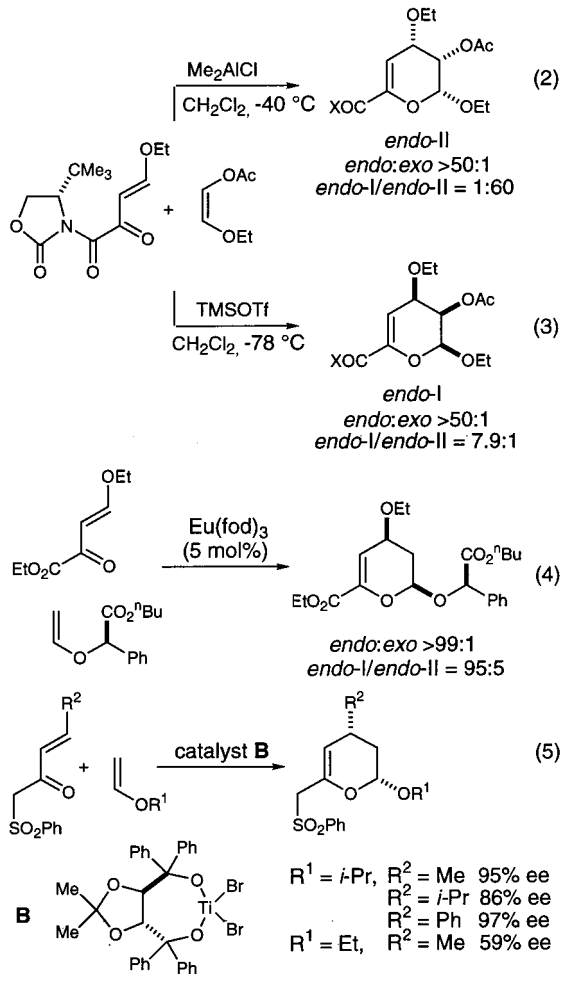
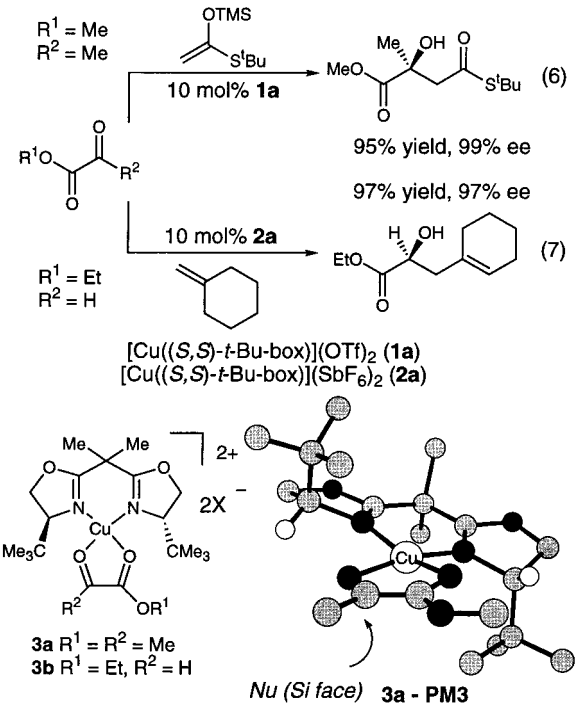
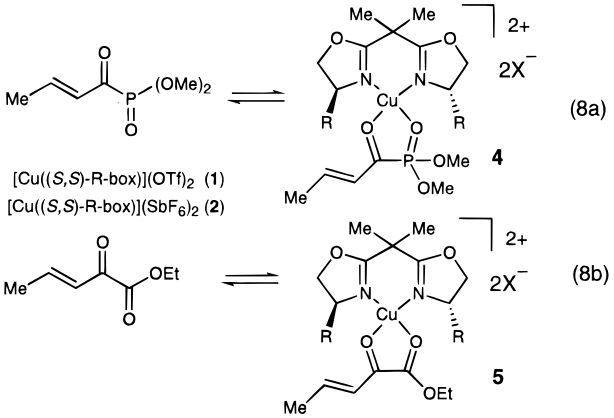


β-oxo-γ,δ-unsaturated sulfones.[8] Isopropyl vinyl ether was found to be a uniquely effective 2π component, facilitating the synthesis of dihydropyrans in good to excellent enantioselectivity using three terminally substituted heterodienes (eq 5).

We were interested in testing the premise that asymmetric catalysis could provide a general solution to the enantioselective synthesis of dihydropyrans. Recent reports from our laboratory have shown that C_2-symmetric bis(oxazoline) (box) copper complexes **1a** and **2a** catalyze enantioselective aldol additions of silyl ketene acetals to pyruvate esters (eq 6) and ene reactions of unactivated olefins and glyoxylate esters (eq 7).[9] Catalyst−substrate complexes **3a** and **3b** were implicated as the species responsible for the observed enantioselection. On the basis of



that work, we speculated that 1-oxa-1,3-butadienes possessing the appropriate activating group at the 2 position could form a similar type of chelated activated intermediate (e.g., **4** and **5**). It had already been shown in independent investigations by Boger and Evans that β,γ-unsaturated α-keto esters and α,β-unsaturated acyl phosphonates participate in hetero Diels−Alder reactions with electron-rich olefins.[10,11] Thus, the phosphonate and ester groups should fulfill the dual criteria of activating the substrate for cycloaddition (by lowering the heterodiene LUMO) and providing a second "docking point" for coordination to the chiral copper(II) Lewis acid. The chiral environment afforded by the bis(oxazoline) ligand was expected to confer reasonable levels of enantioselection in the cycloaddition event (eq 1). The realization of this prediction has provided a general entry into the efficient enantioselective construction of dihydropyrans, a conclusion that has also been reached by Jørgensen and co-workers.[12] The full details of our investigation, including scope, applications, and mechanistic studies, are reported herein.[13]



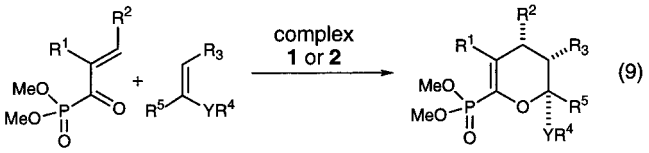
Acyl Phosphonate Cycloadditions

The initial phase of this investigation focused on hetero Diels−Alder reactions of acyl phosphonates with electron-rich alkenes catalyzed by [Cu(box)]X_2 complexes **1** and **2** (eq 9).

(6) For other examples of auxiliary-controlled intermolecular inverse electron demand hetero Diels−Alder reactions, see: (a) Dondoni, A.; Kniezo, L.; Martinkova, M.; Imrich, J. *Chem. Eur. J.* **1997**, *3*, 424. (b) Degaudenzi, L.; Apparao, S.; Schmidt, R. R. *Tetrahedron* **1990**, *46*, 277. (c) Snider, B. B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908. (d) Sato, M.; Sunami, S.; Kaneko, C.; Satoh, S. I.; Furuya, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1665 and references therein. (e) Lopez, J. C.; Lameignere, E.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1988**, 514. (f) Hayes, P.; Dujardin, G.; Maignan, C. *Tetrahedron Lett.* **1996**, *37*, 3687. (g) Wallace, T. W.; Wardell, I.; Li, K. D.; Challand, S. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1707. (h) Haagzeino, B.; Schmidt, R. R. *Liebigs Ann. Chem.* **1990**, 1197.

(7) Enantioselective intramolecular inverse electron demand hetero Diels−Alder reactions catalyzed or promoted by a chiral Lewis acid: (a) Desimoni, G.; Faita, G.; Righetti, P.; Sardone, N. *Tetrahedron* **1996**, *52*, 12019. (b) Narasaka, K.; Hayashi, Y.; Shimada, S.; Yamada, J. *Isr. J. Chem.* **1991**, *31*, 261 and references therein. (c) Tietze, L. F.; Saling, P. *Synlett* **1992**, 281.

(8) (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637. See also: (b) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205. (c) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 145.



(9)

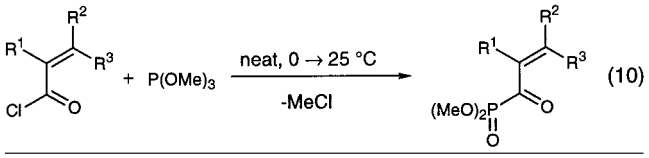
Substrate Synthesis. The Michaelis−Arbuzov reaction provides a convenient approach to the synthesis of acyl phosphonates.[14] Treatment of a number of α,β-unsaturated acid chlorides with trimethyl phosphite (neat, 0→25 °C; CAUTION: chloromethane evolution) afforded unsaturated acyl phosphonates as yellow liquids in variable yield after low pressure distillation directly from the reaction pot (Table 1). Since both the starting material and product are good conjugate acceptors, addition of a second equivalent of phosphite accounted for low yields in some cases (entries 1−3).[15] The tiglic acid-derived acyl phosphonate (entry 5) and the β,β-disubstituted variant (entry 6) were both formed in reasonably good yield, perhaps as a result of steric bulk which reduces the intervention of the undesired reaction pathway. The β,β-disubstituted substrate **6f** was obtained as a mixture of isomeric products (entry 6, *E*:*Z* 2.7:1). In the case of β-alkoxy substrate **6d** (entry 4), electronic deactivation of the β carbon could account for the higher product yield.

Attempts to employ the Arbuzov reaction to synthesize cinnamic acid-derived acyl phosphonate **6b** were largely unsuccessful under a variety of conditions.[16] Recourse was found in an efficient two-step procedure that entailed base-promoted addition of dimethyl phosphite to cinnamaldehyde[17] and oxidation of resultant allylic alcohol under Parikh−Doering conditions (eq 11).[18] Both methods described were amenable to multigram preparation of acyl phosphonates.

The product acyl phosphonates could be stored for months under inert atmosphere at −20 °C and could also be purified by rapid flash chromatography; however, some hydrolysis to the corresponding carboxylic acid was always observed. This contaminant was easily removed with an aqueous bicarbonate wash to give the pure acyl phosphonate; however, in practice chromatography was typically eschewed in favor of distillation.

Catalyst Survey. Crotonyl phosphonate **6a** was added to a solution of the appropriate cationic copper(II) catalyst[19] (10 mol %, CH_2Cl_2) at −78 °C, followed by 3.0 equiv of freshly distilled ethyl vinyl ether (eq 12). The unpurified cycloadduct was isolated at the end of the reaction (TLC analysis) by filtration through silica gel or standard aqueous workup,[20] and after flash chromatography, dihydropyran **7a** was obtained in good to excellent yield. NMR experiments established the Me−OEt cis relationship arising from an endo transition state. The acetal proton at C-2 exhibited a small coupling constant (J_{2-3eq} = 2.3 Hz) with the pseudoequatorial C-3 proton and a larger one with the pseudoaxial C-3 proton (J_{2-3ax} = 6.8 Hz); those values are consistent with other 2,4-substituted cis dihydropyrans.[8b] The observation of NOE enhancements between the C-2 and C-4 protons confirmed the syn relationship of the two substituents.

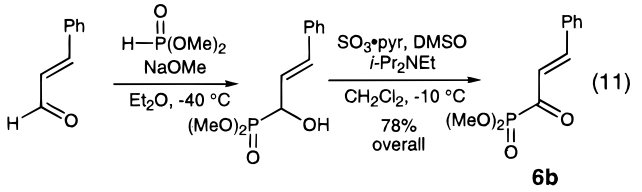
Table 1. Arbuzov Reactions for Synthesis of Acyl Phosphonates (Eq 10)



(10)

entry	product	R^1	R^2	R^3	% yield
1	**6a**	H	Me	H	27
2	**6b**	H	Ph	H	<10
3	**6c**	H	*i*-Pr	H	42
4	**6d**	H	OEt	H	79
5	**6e**	Me	Me	H	84
6	**6f**[a]	H	Et	Me	71

[a] *E*/*Z* = 2.7:1.



(11)

The enantiomeric excess and absolute stereochemistry for **7a** varied with the pendant oxazoline substituent R and counterion X. High enantioselectivity was observed for [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a**, while changing to the less associating counterion SbF_6 (**2a**) resulted in a slight diminution in enantiomeric excess. Lower enantioselection was observed when the oxazoline substituent R was changed from *tert*-butyl to isopropyl (**2c**) or benzyl (**2d**), but [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes **1b** (X = OTf) and **2b** (X = SbF_6) were both highly selective. Chiral HPLC analysis indicated that the major enantiomer produced by [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes **1a** or **2a** was opposite to the one obtained with all other catalysts. The absolute stereochemistry was subsequently established by chemical methods to be that shown in Table 2 (vide infra).

While phenyl- and *tert*-butyl-substituted catalysts confer similar levels of enantioselection, a marked difference in their reactivity has been noted. Specifically, [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a** effects complete conversion in 48 h at −78 °C (eq 12), while [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ complex **1b** requires only 4 h at the same temperature. The complexes possessing the hexafluoroantimonate counterion (**2**) were uniformly more reactive than those complexes with the triflate anion (**1**), in accord with previous findings from our laboratory (e.g., **1a**, 48 h; **2a**, 22 h).[21]

(9) (a) Evans, D. A.; Kazlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

(10) (a) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373. (b) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793.

(11) (a) Schuster, T.; Evans, S. A. *Phosphorus Sulfur Silicon Relat. Elem.* **1995**, *103*, 259. (b) Telan, L. A.; Poon, C. D.; Evans, S. A. *J. Org. Chem.* **1996**, *61*, 7455.

(12) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2404.

(13) A portion of this work has been previously communicated: (b) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (b) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3372. (c) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879.

(14) Karaman, R.; Goldblum, A.; Breuer, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 765 and references therein.

(15) Szpala, A.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1363.

(16) Among those tried: $P(OMe)_3$, PhMe, 0 °C (ref 11a); $P(OMe)_2$(OTMS), PhMe, 0 °C (Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467).

(17) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109.

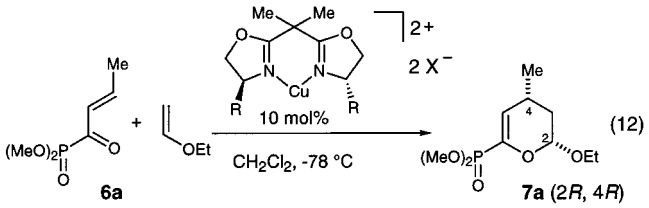
(18) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(19) Cationic copper(II) complexes were prepared as described previously. See: (a) Reference 9b. (b) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

(20) Washing the organic layer with aqueous NH_4OH sequesters the Cu(II) and allows for recovery of the ligand. Assays of diastereomeric and enantiomeric excess were performed prior to flash chromatography.

(21) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

Table 2. Effect of Ligand and Counterion in the Catalyzed Hetero Diels−Alder Reaction (Eq 12)



entry	R	X	endo/exo[a]	% ee (config.)[a]
1	*t*-Bu (**1a**)	OTf	99:1	99 (2*R*,4*R*)
2	*t*-Bu (**2a**)	SbF_6	69:1	93 (2*R*,4*R*)
3	*i*-Pr (**2c**)	SbF_6	32:1	39 (2*S*,4*S*)
4	Bn (**2d**)	SbF_6	60:1	58 (2*S*,4*S*)
5	Ph (**2b**)	SbF_6	>99:1	93 (2*S*,4*S*)
6	Ph (**1b**)	OTf	>99:1	94 (2*S*,4*S*)

[a] Diastereomeric and enantiomeric excesses were determined by chiral HPLC. Product absolute configuration was established by chemical correlation with a compound of known stereochemistry (vide infra).

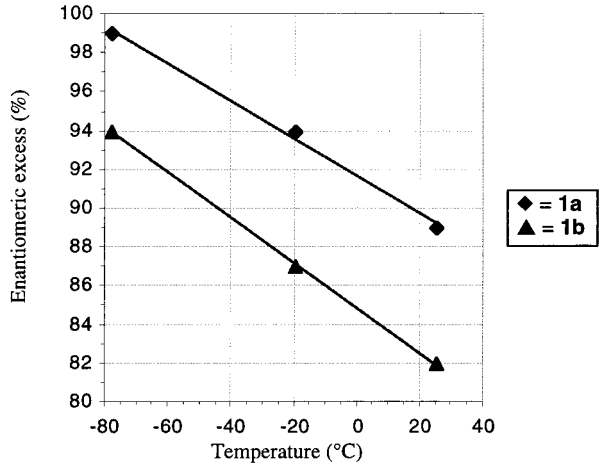
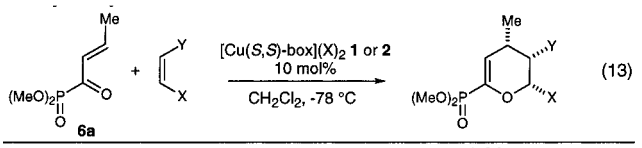
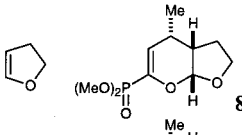
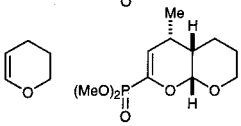
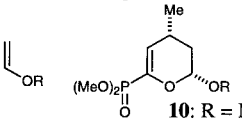
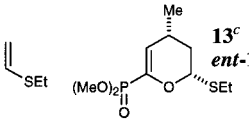


Figure 1. Temperature−enantioselectivity profile for the reaction of phosphonate **6a** and ethyl vinyl ether catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a** and [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ complex **1b** (eq 12).

Reaction Optimization. On the basis of precedent,[9] we hoped that synthetically useful levels of enantioselection might be maintained at more practical laboratory temperatures. As evidenced by the data (Figure 1), [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**1a**) and [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ (**1b**) are capable of delivering cycloadduct of high enantiomeric excess even at room temperature. Predictably, shorter reaction times are possible: the reaction of **1a** at −20 °C reaches completion in less than 3 h, while **1b** catalyzes the reaction to completion very rapidly (<5 min) at 25 °C. The speed of the reaction coincides with an exotherm that is noticeable even on fairly small scale (0.3 mmol). Indeed, we noted in our initial report that catalyst decomposition (brown reaction solution) and low conversion had been noted for [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ complex **1b** at 25 °C; this problem has been circumvented simply by introducing the enol ether slowly (10 min) into the reaction vessel, allowing for complete conversion to product and retention of the complex's characteristic green color. The thermally induced decomposition described above has not been noted in any other aspects of this investigation and careful monitoring of the internal temperature of preparative-scale (ca. 20 mmol) reactions at low temperature (<−70 °C) reveals that the reaction does not produce any appreciable exotherm (<3 °C over 10-min addition).

Table 3. Cycloadditions of Crotonyl Phosphone **6a** with Enols Catalyzed by **1** and **2** (Eq 13)



hetero dieneophile	product (*endo*/*exo*)[a]		catalyst	yield (%)	% ee[a]
	**8a**[b]	(>99:1)	**1a**	91	95
	**9**[c]	(62:1)	**2a**	55	92
		(13:1)	**2a**[d]	100	89
	**10**: R = Me[e]	(70:1)	**2a**	nd	85
	***ent*-10**	(>99:1)	**2b**	95	86
	11: R = *t*-Bu[e]	(1.3:1)	**2a**	35	66 (80)[h]
		(10:1)	**2b**	100	2 (55)[h]
	12: R = TBS[f]	(1:1)	**2a**[g]	nd	64 (26)[h]
	**13**[c]	(>20:1)	**2a**	31	76
	***ent*-13**	(150:1)	**2b**	89	95

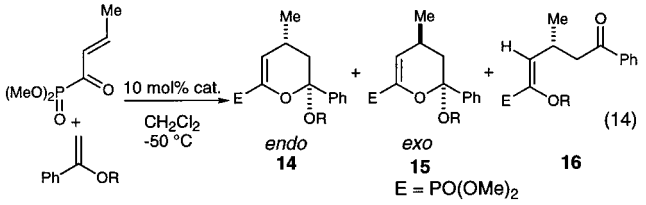
[a] Determined by capillary GLC or chiral HPLC. [b] Absolute configuration established by X-ray crystallographic analysis of a derivative (vide infra). [c] Absolute configuration assigned by analogy. [d] Reaction conducted at −40 °C. [e] Absolute stereochemistry was established by chemical correlation to compounds of known absolute configuration (vide infra). [f] Relative and absolute configuration not assigned. % ee is for the major diastereomer. [g] Reaction conducted at −20 °C. [h] % ee of minor diastereomer.

To further probe the practicality of the reaction, a systematic evaluation of the effect of catalyst loading was conducted. The attenuated reactivity of [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ complex **2a** relative to [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$ complex **2b** was apparent in these experiments as well, since reducing the amount of **2a** resulted in stalled reactions and incomplete conversion to product even upon warming to −20 °C. In contrast, **2b** was amenable to substantially reduced catalyst loadings. Dihydropyran **7a** was obtained in 95% yield after 16 h at −78 °C using 1 mol % of **2b**; no change in enantioselectivity was observed at this lower catalyst loading. As an added advantage, it was possible to conduct the reactions at substrate concentrations up to 1.2 M. At that concentration, complete conversion to the cycloadduct was realized employing only 0.2 mol % **2b** at a slightly elevated temperature (−50 °C). The yield and enantioselectivity were unchanged (93% yield, 93% ee), but the protracted reaction time (62 h) signals that this is realistically the lower limit for catalyst loadings in this reaction. Despite that limitation, it is noteworthy that 3.6 mg of the chiral ligand was sufficient to deliver 1.24 g of the enantioenriched product.

Heterodienophile Scope. A representative selection of electron-rich alkenes was tested in the catalyzed cycloaddition with crotonyl phosphonate **6a** as part of an effort to define the scope of the reaction (Table 3).

The synthesis of bicyclic adducts **8a** and **9** in high diastereomeric and enantiomeric excess signals that cyclic enol ethers are well tolerated. The reduced reactivity of 2,3-dihydropyran relative to 2,3-dihydrofuran is reflected in the need to conduct

Table 4. Catalyzed Reactions of Crotonyl Phosphonate **6a** with Silyl Enol Ethers of Acetophenone (Eq 14)



cat.[a]	R	product ratio **14**:**15**:**16**	% ee **14**	% ee **15**	% ee **16**
2a	TMS	57:5:38	99	74	70
2b	TMS	18:2:80	97	−9	−5
2a	TBS	93:7:0	99	82	
2b	TBS	60:40:0	96	99	

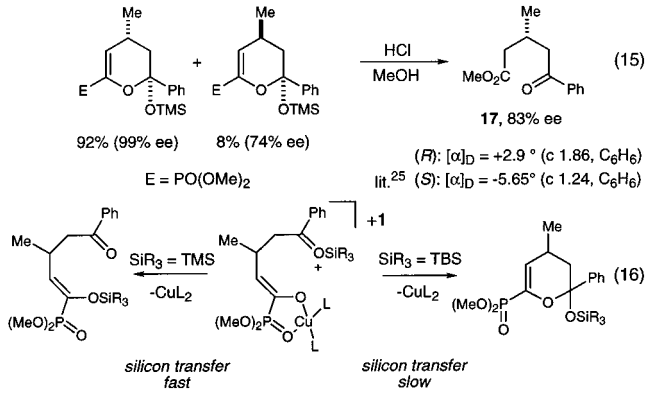
[a] **2a**: [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$. **2b**: [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$.

that cycloaddition at higher temperature to achieve complete conversion.[22] The formation of **8a** and **9** was also catalyzed by [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes; however, enantioselectivities were noticeably lower (for catalyst **1b**: *ent*-**8a**, 89% ee; *ent*-**9**, 52% ee).

The initial results obtained with ethyl vinyl ether were shown to be optimal for monosubstituted alkenes (Table 3); however, the dependence of the diastereo- and enantioselectivity on the size of the enol subsituent provided valuable insight into the nature of the reaction transition state (vide infra). Methyl vinyl ether reacted with crotonyl phosphonate in the presence of [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ complex **2a** and [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$ complex **2b** to yield cycloadduct **10** and *ent*-**10** in diastereoselectivities that mirror those obtained with ethyl vinyl ether; however, the enantiomeric excesses were slightly lower. *tert*-Butyl vinyl ether exhibited variable selectivity that was catalyst dependent. A complete collapse of endo selectivity was found using **2a**, while good levels of endo diastereoselection were maintained using **2b**. Enantioselectivities were considerably lower for this heterodienophile relative to methyl and ethyl vinyl ether. Low selectivity and reactivity were also noted for *tert*-butyldimethylsilyl vinyl ether. Ethyl vinyl sulfide induced no noticeable decomposition of the transition metal catalyst and was in fact a highly selective participant in the cycloaddition with **6a** to give **13** and *ent*-**13**, the latter in especially good yield and selectivity. Vinyl acetate produced no cycloadduct with **6a** even at 25 °C, while styrene reacted only slowly, producing a 21% yield of the derived cycloadduct after 5 d at 25 °C (**2a**, dr 4.5:1). The cycloaddition of crotonyl phosphonate **6a** and α-trimethylsiloxy styrene was attempted to assess the viability of 1,1-disubstituted enol ethers (eq 14, R = TMS).[11b] For [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ complex **2a**, the major reaction pathway was the formal cycloaddition to form both cis and trans (Me↔OTMS) dihydropyrans **14** and **15**, while the minor pathway resulted in the formation of Michael adduct **16**.[23] The endo isomer **14** was formed preferentially using either **2a** and **2b**, with virtually complete π-facial selectivity observed for both catalysts (99% and 97% ee, respectively). In contrast to those results obtained with monosubstituted enol ethers, the facial bias conferred by **2a** and **2b** was identical: *the same product enantiomer was formed for both the phenyl and tert*-butyl bis(oxazoline) Cu(II) catalysts.

Silyl enol phosphonate **16** was obtained as a single geometric isomer (>20:1 *E*:*Z*, ^{1}H NMR) that was assigned the illustrated stereochemistry by the observation of a characterizic J_{H-P} coupling of 10.0 Hz for the vinyl proton.[24] The observation of the (*E*) product geometry implicates a reactive *s*-cis acyl phosphonate conformation: accepting a nucleophile from the *s*-trans conformation would lead to the formation of the (*Z*) isomer. Unfortunately, the (*Z*) enol was never observed, so it was not possible to conclude whether **16** was the kinetic or thermodynamic product (or both).

The cycloadducts **14**/**15** were separated from the Michael adduct **16** by flash chromatography and treated with anhydrous HCl/MeOH to give (*R*)-methyl 3-methyl-5-oxo-5-phenylpentanoate (**17**), a compound of known absolute configuration (eq 15).[25] If isomers **14** and **15** possessed the same absolute configuration at C-4, the enantiomeric excess of the derived keto ester would be 96% (12:1 isomer ratio → 92% of 99% ee material and 8% of 74% ee material). The observed enantioselectivity (83%, HPLC) indicated that the two diastereomeric cycloadducts possessed the *opposite* configuration at the methyl-bearing stereocenter. The absolute configuration of Michael adduct **16** was also assigned by chemical conversion to methyl ester **17** and was found to be the same as that of the major cycloadduct **14** (*R*).



While alteration of the reaction conditions (solvent, temperature) did little to affect the product distribution, effective channeling of the reaction through the cycloaddition manifold was realized by changing the oxygen protecting group from TMS to TBS. Silyl transfer to a putative Cu(II) enolate is presumably retarded using the bulkier silyl group and the formal cycloaddition pathway becomes dominant, strongly implicating a nonconcerted reaction for this heterodienophile (eq 16). Good enantiocontrol was again realized for both [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ complex **2a** and [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$ complex **2b**; however, the latter catalyst suffered a rather precipitous drop in diastereoselectivity.[26] Despite this fact, the formation of both diastereomeric products proceeded with high enantioselectivity.

Other ketone-derived enol ethers were tested, but the results

(22) By way of comparison, the reactivity of ethyl vinyl ether is intermediate to dihydropyran and dihydrofuran. Since these reactions may reasonably be assumed to proceed through a concerted, but asynchronous transition state (vide infra), a correlation between heterodienophile reactivity and enol ether nucleophilicity might be expected. The observed trend betweeen dihydrofuran and dihydropyran is consistent with the Mayr nucleophilicity scale, but ethyl vinyl ether was reported to be less nucleophilic than dihydropyran: Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938.

(23) The cycloadduct **14**/**15** and Michael adduct **16** do not interconvert upon independent resubjection to catalyst **2a**.

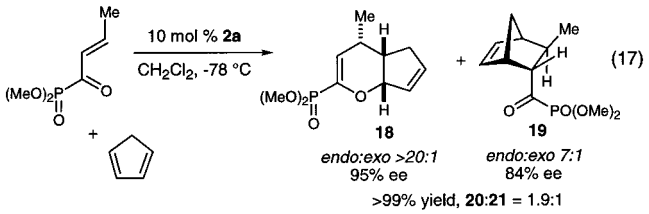
(24) Afarinkia, K.; Echenique, J.; Nyburg, S. C. *Tetrahedron Lett.* **1997**, *38*, 1663.

(25) (a) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967. (b) Shi, Y.; Wulff, W. D.; Yap, G. P. A.; Rheingold, A. L. *Chem. Commun.* **1996**, 2601.

(26) In this case, the diastereoisomeric products were separated by preparative HPLC. Dihydropyran **14** (R = TBS, 96% ee) was subjected to acidic MeOH.; the enantiomeric excess of the product keto ester **17** was also 96%.

were uniformally mediocre.[27] For reasons that are not known, the use of the more electron-rich TMS-ketene acetal of *tert*-butylthioacetate resulted in low conversion to product. A 30% yield of a 1.8:1 mixture of cycloadduct and Michael adduct was obtained with this olefin.

The need for heteroatom activation of the 2π component is not mandatory, as evidenced by the results obtained for the reaction of cyclopentadiene and **6a** (eq 17). Under the influence



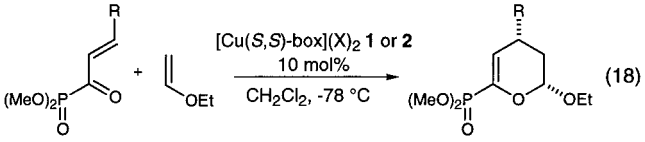
(17)

of **2a**, a separable 1.9:1 mixture of hetero [4+2] and normal [4+2] adducts was obtained.[28] The hetero Diels−Alder product **18** was obtained as a single regio- and diasteroisomer (^{1}H NMR) in 95% ee. The alternate reaction manifold was less selective, with the bridged bicyclic product **19** formed in 7:1 endo:exo selectivity and 84% ee (endo).[29] Adducts **18** and **19** are potentially related to each other by a [3,3] sigmatropic rearrangement;[28b] however, a control experiment indicated that under the conditions of the reaction, no product interconversion is occurring. A qualitative comparison of the electrophilicity of unsaturated acyl phosphonates and unsaturated acyl oxazolidinones is now possible. The reaction illustrated in eq 17 was complete in 1 h at −78 °C, while the corresponding catalytic Diels−Alder reaction with the crotonyl oxazolidinone requires 8 h at 25 °C.[30]

Heterodiene Scope. The other reaction partner in this Diels−Alder reaction was next considered. In contrast to the 2π moiety, virtually every permutation of α,β-unsaturated acyl phosphonate led to a highly selective cycloaddition reaction.

With respect to simple β-substituted α,β-unsaturated acyl phosphonates, broad substrate generality was enjoyed. In particular, phenyl-, isopropyl-, and ethoxy-substituted substrates all participated in high yielding, diastereoselective Diels−Alder reactions with ethyl vinyl ether to give dihydropyrans **7b**−**d** (Table 5). The enantioselectivities were consistently excellent for both **2a** and **2b**; however, protracted reaction times and incomplete conversion were observed for the formation of **7b** and **7c** using *tert*-butyl substituted **2a**. Our general preference is to employ [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes **1b** (X = OTf) or **2b** (X = SbF_6) when possible due to the heightened reactivity

Table 5. Hetero Diels−Alder Reactions of Acyl Phosphonates and Ethyl Vinyl Ether Catalyzed by **1** and **2** (Eq 18)



(18)

2a: [Cu((*S*,*S*)-*t*-Bu-box)](SbF_6)$_2$; **2b**: [Cu((*S*,*S*)-Ph-box)](SbF_6)$_2$

product	catalyst	% yield	endo/exo[a]	% ee[a]
7b: R = Ph[b]	**2a**	88	32:1	94
ent-**7b**	**2b**	98	>99:1	98
7c: R = *i*-Pr[b]	**2a**	78	32:1	93
ent-**7c**	**2b**	99	>99:1	96
7d: R = OEt[c]	**2a**	96	>99:1	93
ent-**7d**	**2b**	49	99:1	77

[a] Determined by capillary GLC or chiral HPLC. [b] Absolute stereochemistry was established by chemical correlation to compounds of known absolute configuration (vide infra). [c] Absolute configuration assigned by analogy.

of those catalysts relative to [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes **1a** and **2a**. To effect complete conversion to **7d** with catalyst **2a**, it proved necessary to employ a large excess of ethyl vinyl ether (10 equiv) due to competing polymerization of that reaction component, presumably catalyzed by the electrophilic Lewis acid. Fortunately, this competing reaction is not a general phenomenon.

To assess the preparative utility of the hetero Diels−Alder reaction, the catalyzed cycloaddition of 5.17 g of cinnamoyl phosphonate **6b** with ethyl vinyl ether was conducted in the presence of [Cu((*S*,*S*)-Ph-box)](SbF_6)$_2$ complex **2b** (2.5 mol %), delivering after 22 h, 6.27 g (98% yield) of *ent*-**7b** in 98% ee and virtually complete diastereoselection (endo/exo > 150:1, GLC). No special measures are required for the reaction, indicating the feasibility of producing such enantioenriched dihydropyrans on a reasonable laboratory scale.

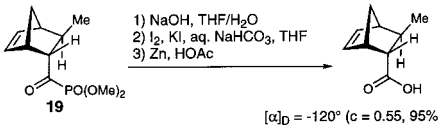
Bicyclic adducts **8b**−**d** were also formed in good yields and selectivities under the influence of bis(oxazoline) Cu(II) complexes (Table 6). It was feasible in some cases to employ the less reactive triflate-derived catalysts due to the heightened reactivity of dihydrofuran relative to ethyl vinyl ether. In contrast to our carbocyclic Diels−Alder studies, we have found that triflate catalysts **1a** and **1b** typically give products whose enantiomeric excess is 5−10% higher relative to those obtained using hexafluorantimonate-derived **2a** or **2b**.

The acyl phosphonate derived from tiglic acid (**6e**) participated in diastereo- and enantioselective Diels−Alder reactions with ethyl vinyl ether to give a dihydropyran (**20**) substituted at four of the five ring carbon atoms; however, the attenuated reactivity of this substrate led to low yields as a result of incomplete conversion when [Cu((*S*,*S*)-*t*-Bu-box)](SbF_6)$_2$ com-

(27) Among those tried: 2-methoxypropene (**1a**, dr 4.5:1, 72 and 37% ee; **2b**, dr 6.9:1, −57 and −38% ee), 2-trimethylsiloxypropene (**2a**, dr 1.7:1, 43% ee), 1-cyclohexyl-1-trimethylsiloxyethylene (low conversion), α-methoxy styrene (**2a**, dr 2.4:1, 86 and 72% ee; **2b**, dr 2.4:1, 36 and 49% ee). For these enol ethers, only the dihydropyran product was obtained.

(28) Instead of reporting that this was the first *enantioselective* example of cyclopentadiene behaving as a dieneophile with an α,β-unsaturated carbonyl, our initial communication stated only that this was the first example. We thank Prof. S. Hanessian for alerting us to this error and calling to our attention this example: (a) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, 4098. In that case the normal Diels−Alder adduct was preferred (5:1). In our case, we note that when the reaction is conducted thermally (neat), the normal [4+2] pathway is preferred (2:1). To our knowledge, the first examples of cyclopentadiene acting as a dieneophile in hetero Diels−Alder reactions with α,β-unsaturated carbonyls were reported in 1982: (b) Ismail, Z. M.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 859. (c) Dvorák, D.; Arnold, Z. *Tetrahedron Lett.* **1982**, *23*, 4401.

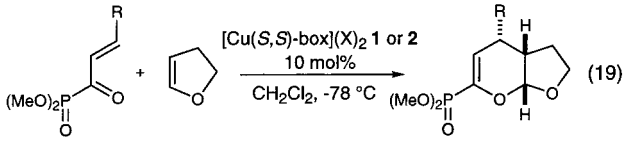
(29) The absolute configuration of **19** was established through chemical correlation to the corresponding carboxylic acid of known absolute configuration: (a) Berson, J. A.; Bergman, R. G.; Hammons, J. H.; McRowe, A. W. *J. Am. Chem. Soc.* **1967**, *89*, 2581. (b) Berson, J. A.; Hammons, J. H.; McRowe, A. W.; Bergman, R. G.; Remanick, A.; Houston, D. *J. Am. Chem. Soc.* **1967**, *89*, 2590.



$[\alpha]_D$ = -120° (c = 0.55, 95% EtOH)
lit. $[\alpha]_D$ = -157° (95% EtOH)

(30) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.

Table 6. Hetero Diels−Alder Reactions of Acyl Phosphonates and 2,3-Dihydrofuran Catalyzed by **1** and **2** (Eq 19)

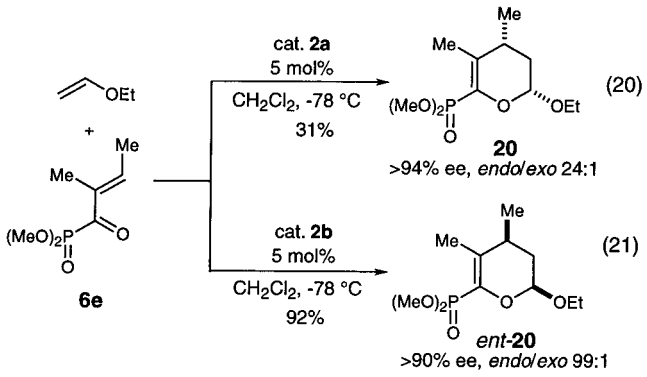


2a: [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$; **1b**: [Cu((*S*,*S*)-Ph-box)](OTf)$_2$

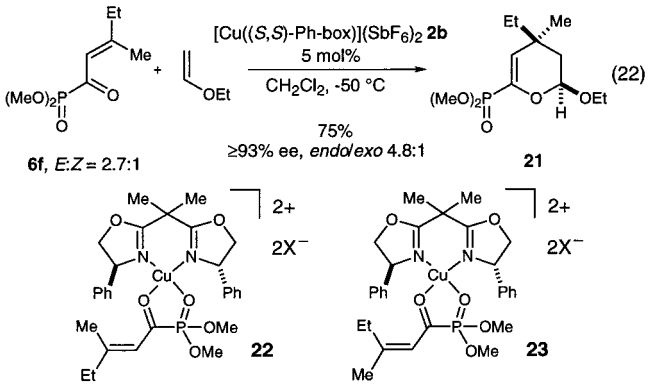
product	catalyst	% yield	endo/exo[a]	% ee[a]
8b: R = Ph[b]	**2a**	99	(>99:1)	90
ent-**8b**	**1b**	98	(>99:1)	94
8c: R = *i*-Pr[b]	**2a**	79	(49:1)	90
ent-**8c**	**2b**	94	(>99:1)	71
8d: R = OEt[b]	**2a**	98	(>99:1)	97
ent-**8d**	**1b**	100	(>99:1)	84

[a] Determined by capillary GLC or chiral HPLC. [b] Absolute configuration assigned by analogy.

plex **2a** was employed (eq 20). This problem was circumvented by using the more reactive [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$ complex **2b** (eq 21).



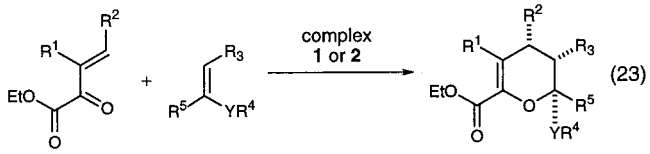
The β-ethyl-β-methyl-substituted acyl phosphonate **6f**, as noted in the discussion of substrate preparation, was synthesized as a 2.7:1 mixture of geometric isomers. When that isomeric mixture was treated with ethyl vinyl ether in the presence of [Cu((*S*,*S*)-Ph-box)](SbF$_6$)$_2$ **2b**, an inseparable diasteromeric mixture of cycloadducts was obtained in 75% yield (eq 22).



On the basis of NOE enhancements between the acetal proton and the Me group at the quaternary carbon, the identity of the major isomer was established as dihydropyran **21**, with the Et and OEt moieties disposed cis to one another on the six-membered ring.[31] Importantly, the 2.7:1 mixture of geometric isomers in the starting material was not reflected in the 4.8:1 mixture of diastereomers in the product. A control experiment in which the unsaturated acyl phosphonate was incubated with the catalyst in the absence of any heterodienophile demonstrated that the recovered heterodiene had the same isomeric composition as the starting material. To account for the observed results, we propose that the reaction is under Curtin−Hammett control whereby the chiral Lewis acid induces an isomerization of the starting material, the activation energy of which is low relative to the activation energy for the cycloaddition reactions.[32] This (*E*)/(*Z*) isomerism presumably proceeds through the intermediacy of activated complexes **22** and **23**. An endo-selective cycloaddition of **22** and ethyl vinyl ether accounts for the formation of the major diastereomer.[33] The chiral Cu(II) Lewis acid is apparently able to make the subtle distinction between the methyl and ethyl groups. In contrast, the use of $TiCl_4$ as a promoter gave **21** as a 1.2:1 mixture of diastereoisomers.

α-Keto Ester Cycloadditions

Given the successful application of catalysts **1** and **2** to the hetero Diels−Alder reactions of acyl phosphonates and enol ethers, the analogous series of experiments in the α-keto ester series was investigated (eq 23).



Substrate Synthesis. Substituted β,γ-unsaturated α-keto esters were accessed by a modified method of Sugimura.[34] Boron trifluoride-promoted aldol reactions between the trimethylsilyl enol ether of ethyl pyruvate and the appropriate dimethyl acetals afforded the derived ethers. Treatment of the unpurified adducts with Florisil (benzene, 25 °C) induced elimination to provide unsaturated keto esters **24a**−**c** (Scheme 1, eq 24).

γ-Ethoxy substrate **24e** could be prepared according to Tietze's method through the reaction of ethyl vinyl ether and ethyl chlorooxalate (neat),[35] but was obtained in higher yield using triethylamine and catalytic amounts of Pd(OAc)$_2$ (Scheme 1, eq 25).[5a] The γ-methoxy variant **24d** could only be obtained by the latter method since the thermal reaction did not occur at the reflux temperature of methyl vinyl ether (5−6 °C). The γ-ethoxy keto ester **24e** underwent smooth transetherification with benzyl mercaptan under mild conditons (Scheme 1, eq 26) to give γ-thiobenzyl keto ester **24f** as a mixture of geometric isomers that were separated by flash chromatography. The γ-methyl-β,γ-unsaturated α-keto Weinreb amide **25a** was prepared by monoaddition of 1-propenylmagnesium chloride to the bis-Weinreb amide of oxalic acid (eq 27),[36] while the

(31) For approaches to the synthesis of quaternary carbon stereocenters, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

(32) For a relevant example, see: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. For an example of a catalytic asymmetric reaction under Curtin−Hammett control, see: (b) Halpern, J. *Science* **1982**, *217*, 401.

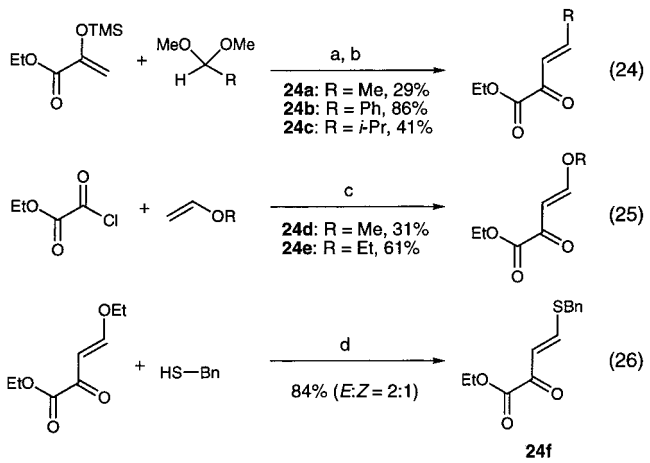
(33) Alternatively, the major diastereoisomer could be formed through an exo selective cycloaddition through the intermediacy of complex **23**. Since the endo transition state is favored for every catalyzed reaction studied with ethyl vinyl ether, we do not favor this analysis. In theory, employing a group larger than ethyl should further amplify the proposed Curtin−Hammett effect; in practice, the β-methyl-β-isopropyl substrate is unreactive. No reaction was observed with **6f** using catalyst **2a**.

(34) Sugimura, H.; Yoshida, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3209.

(35) Tietze, L. F.; Meier, H.; Voss, E. *Synthesis* **1988**, 274.

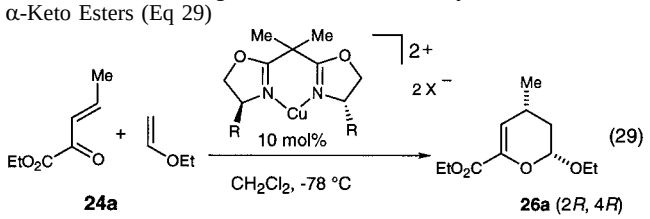
(36) Sibi, M. P.; Marvin, M.; Sharma, R. *J. Org. Chem.* **1995**, *60*, 5016.

Scheme 1[a]



[a] Reaction conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C; (b) Florisil, C_6H_6, 25 °C; (c) $Pd(OAc)_2$ (cat.), Et_3N; (d) cat. $KHSO_4{\cdot}H_2O$, 30 Torr.

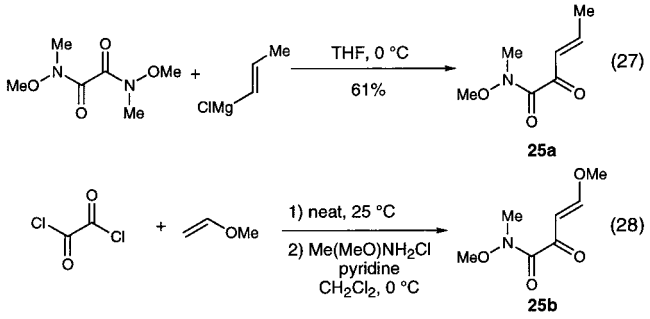
Table 7. Effect of Ligand and Counterion in Cycloadditions of α-Keto Esters (Eq 29)



entry	R	X′	endo/exo[a]	% ee (config.)[a]
1	*t*-Bu (**1a**)	OTf	49:1	95 (2*R*,4*R*)
2	*t*-Bu (**2a**)	SbF_6	1.3:1	95 (2*R*,4*R*)
3	*i*-Pr (**1c**)	OTf	24:1	38 (2*R*,4*R*)
4	Bn (**1d**)	OTf	24:1	39 (2*R*,4*R*)
5	Ph (**1b**)	OTf	20:1	56 (2*S*,4*S*)

[a] Diastereomeric and enantiomeric excesses were determined by chiral HPLC. The absolute configuration was assigned by analogy to related compounds (vide infra).

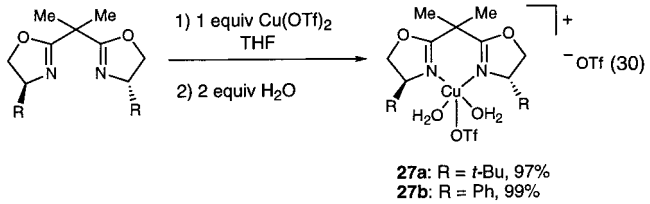
γ-methoxy variant **25b** was synthesized through amination of the appropriate α-keto acid chloride (eq 28, unoptimized).



The keto esters were purified by flash chromatography and stored under argon atmosphere at −20 °C. Some decomposition of the γ-alkoxy compounds was noted over time. Optimal results with these substrates were obtained when the keto ester was purified immediately prior to use.

Catalyst Survey. The reaction of *E*-ethyl 2-oxo-3-pentenoate **24a** with ethyl vinyl ether in the presence of [Cu((*S*,*S*)-*t*-Bu-box)]$(OTf)_2$ complex **1a** (10 mol %, CH_2Cl_2, −78 °C) led to the formation of dihydropyran **26a** in good yield and excellent stereoselectivity (Table 7). The enantioselectivity afforded by the more reactive SbF_6-derived **2a** was identical with that of the triflate catalyst (95% ee), but the diastereoselection was surprisingly low (1.3:1). While the reversal in enantioselectivity was also noted for this substrate employing [Cu((*S*,*S*)-Ph-box)]$(SbF_6)_2$ complex **2a** (−56% ee), the level of asymmetric induction was not comparable to the *tert*-butyl variant. In contrast to the results in the acyl phosphonate cycloadditions, [Cu((*S*,*S*)-*i*-Pr-box)]$(OTf)_2$ complex **1c** and [Cu((*S*,*S*)-Bn-box)]$(OTf)_2$ complex **1d** afforded the same product enantiomer as **1a**. Initial attempts to expand the scope of the reaction to other heterodienes were unsuccessful: the reaction of the γ-phenyl-β,γ-unsaturated-α-oxo ester **24b** with ethyl vinyl ether under identical conditions gave the corresponding cycloadduct in only 78% ee. Examination of other reaction variables appeared warranted at this juncture.

Reaction Optimization. We first decided to take advantage of observations made previously in our laboratory during investigations of the aldol and carbocyclic Diels−Alder reactions.[37] A key finding in those studies was that the use of aquo complex **27a** in the presence of 3 Å molecular sieves generated a catalyst whose activity and selectivity were identical with those of anhydrous complex **1a**. Aquo complexes **27a** and **27b** were prepared by the addition of 2.0 equiv of water to a THF solution of the corresponding anhydro complex (eq 30). Following solvent removal and trituration with hexane, [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$(OTf)](OTf) complex **27a** and [Cu((*S*,*S*)-Ph-box)-$(H_2O)_2(OTf)_2$] complex **27b** were obtained in high yield as stable light blue solids characterized by elemental analysis and X-ray crystallography.



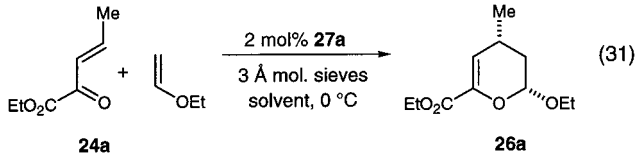
The findings described above potentially define a protocol for streamlining the catalyst preparation, obviating the need to complex the ligand to the metal salt for every reaction. The reduction of this concept to practice was straightforward. Implementation of a protocol wherein the heterodiene and heterodienophile were added to a mixture of [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$(OTf)](OTf) complex **27a** and molecular sieves gave results indistinguishable from those obtained using **1a**. Subsequent control experiments have revealed that **27a** is a poor catalyst for the reaction in the absence of molecular sieves and that catalyst dehydration does not occur to an appreciable extent in the absence of the α-keto ester.[38]

A survey of reaction solvents employing the operationally simplified catalyst preparation demonstrated that dichloromethane was not the optimal reaction solvent (Table 8).[39] A

(37) (a) Reference 9b. (b) Barnes, D. M. Ph.D. Thesis, Harvard University, 1997. For other uses of aquo complexes in catalytic asymmetric reactions, see: (c) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454−6455. (d) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088. (e) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3687−3691.

(38) The reaction of *E*-ethyl-5-methyl-2-oxo-3-hexenoate (**24c**) and ethyl vinyl ether was conducted with catalysts (2 mol %) prepared three different ways: (A) **27a** was stirred for 1 h in THF and the reaction was conducted as normal; (B) **27a** was stirred in the presence of 3 Å molecular sieves for 1 h in THF, after which time the mixture was filtered through an oven-dried 0.2 μm filter into an oven-dried flask. The reaction was conducted as normal; (C) **27a** was stirred in the presence of 3 Å molecular sieves for 1 h in THF and the reaction was conducted as normal. Approximate half-lives for the reactions (0 °C): A, ≈20 h; B, ≈5 h; and C, <5 min.

Table 8. Catalyzed Hetero Diels−Alder Reactions Employing Bis(aquo) Complex **27a** and 3 Å Molecular Sieves (Eq 31)



(31)

24a **26a**

entry	solvent	endo/exo	% ee
1	CH_2Cl_2	19:1	89
2	THF	24:1	97
3	Et_2O	24:1	97
4	toluene	28:1	98
5	dioxane[a]	24:1	93

[a] This reaction run at room temp.

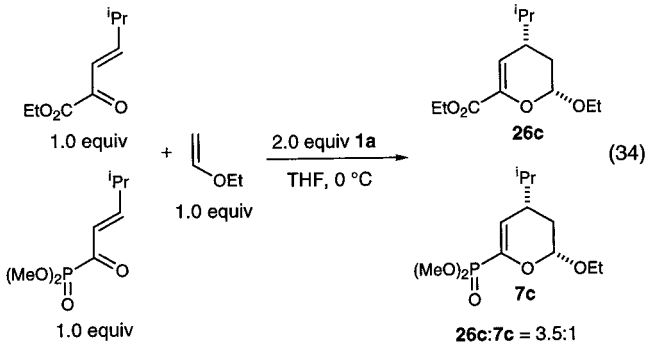
number of solvents functioned well in the reaction, with THF, Et_2O, and toluene all providing selectivities superior to CH_2Cl_2.

Two observations made simultaneously carried important consequences for the practical implementation of subsequent reactions. The first was that nearly complete enantiocontrol could be maintained even at 0 °C. While it was possible to attain enantioselectivities exceeding 99% at lower temperature (−40 °C), the favorable temperature−enantioselectivity profile[40] meant that synthetically useful levels of enantioselection were possible at convenient temperatures. The second finding was that 2 mol % of the Cu(II) complex **27a** was sufficient to catalyze the cycloaddition to completion in less than 1 h. These advantages led us to pursue this protocol in later reactions.

Reaction Scope. The substrate tolerance for this reaction was broad, with uniformly high levels of enantiomeric excess found in the adduct dihydropyrans (Table 9). Alkyl-, aryl-, alkoxy-, and thiobenzyl-substituted heterodienes reacted with ethyl vinyl ether to give **26a**−**f** in 96−99% enantioselection using [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$(OTf)](OTf) complex **27a**. Reaction times were typically 15−45 min at 0 °C. In contrast to the acyl phosphonate reactions with *tert*-butyl-substituted catalysts, reduced catalyst loadings were possible: **26a** was synthesized in high selectivity (19:1 endo:exo, 96% ee) using 0.5 mol % of **27a**. Preparative scale reactions were again straightforward, as 5.0 g of phenyl-substituted keto ester afforded 6.7 g (98%) of **26b** (>99:1 endo:exo, 99% ee) using 2 mol % of **27a**. Dihydrofuran and vinyl sulfides functioned efficiently as heterodienophiles to give **28b**,**c** and **29a**,**b** stereoselectively. We have further found that the substituted β,γ-unsaturated α-keto Weinreb amides were also excellent heterodienes, giving **30a**,**b** with high diastereo- and enantiocontrol.[41] The synthetic advantages of compounds incorporating this moiety have been reviewed.[42]

It appeared likely that the conditions employed in the acyl phosphonate cycloadditions could be optimized considering the results obtained with α-keto esters. Accordingly, the improved reaction conditions were tested for a representative selection of acyl phosphonates. The results of Table 10 unambiguously show that superior results were realized with the simplified reaction protocol.

A 5 mol % catalyst loading of [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$(OTf)](OTf) complex **27a** was needed to effect complete conversion to product in the acyl phosphonate reactions. This requirement was consistent with a competition experiment demonstrating that β,γ-unsaturated α-keto esters were somewhat more reactive that α,β-unsaturated acyl phosphonates in catalyzed cycloadditions (eq 34). A stoichiometric amount of catalyst was employed in this reaction to avoid potential complications arising from different substrate·catalyst binding affinities (eq 8).



(34)

The successful use of a solid catalyst precursor prompted us to consider the possibility of reusing the chiral complex in multiple reaction cycles.[43] When the catalyzed cycloaddition of **24b** and ethyl vinyl ether was conducted with 3 Å molecular sieves and Florisil in hexanes, a solvent in which [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$(OTf)](OTf) complex **27a** is apparently insoluble, a rapid reaction ensued.[44] The supernatant was decanted by syringe after keto ester **24b** was completely consumed (TLC analysis), and the resulting solids were rinsed twice with hexane. Introduction of more reactants led to resumption of the reaction, a cycle that was repeated five times (Table 11). As evidenced by the data, reactivity degrades in progressive reaction cycles; nonetheless, the consistently high yields and selectivities are noteworthy.

Product Elaboration and Stereochemical Proofs

Upon treatment of the adduct dihydropyrans with dry HCl/MeOH, rupture of the acetal linkage and solvolysis of the enol phosphonate ensued to afford the corresponding acetal ester.[45] Without purification, the dimethyl acetal was removed in aqueous acetone with catalytic amounts of pyridinium *p*-toluenesulfonate, giving aldehydic esters in 73−86% yield (R^1 = Me, Ph, *i*-Pr) for the two steps (Scheme 2, steps a and b). Attempts to merge these two steps were generally unsuccessful and application of the protocol to 4-alkoxy-2,3-dihydropyrans (**7d**, R = OEt) was not feasible due to concomitant elimination of the alkoxy group. The products of this solvolysis sequence are Michael adduct equivalents of an aldehyde enolate and β-substituted acrylate ester.

Reduction of the aldehydic moiety followed by acid-catalyzed cyclization yielded the corresponding δ-lactones **32a**,**c**, facilitating unambiguous determination of the absolute configuration of the original cycloadducts by comparison of optical rotations.[46] Those assignments are summarized below.[47]

(39) The reactions were conducted at 0 °C for the sake of simplicity. The higher temperature should also accentuate any differences in enantioselectivity.

(40) Reaction of the phenyl-substituted unsaturated keto ester in THF to give **26b**: −40 °C, >99% ee; −20 °C, 98% ee; 0 °C, 97% ee; and 25 °C, 94% ee.

(41) The authors thank Mr. Jacob M. Janey for performing one of these reactions (**30a**).

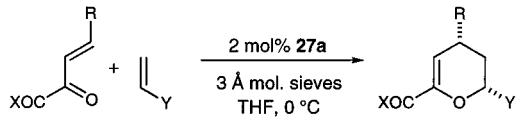
(42) (a) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15−40. (b) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem.* **1997**, *339*, 517−524.

(43) . For an excellent example, see: Hansen, K. F.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.

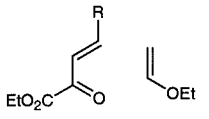
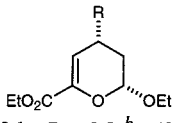
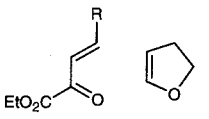
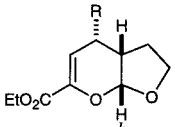
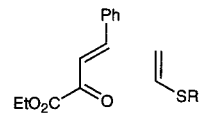
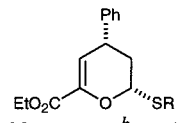
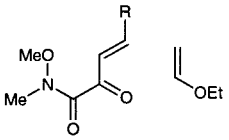
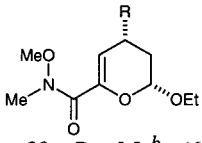
(44) The exact role of the absorbent is not clear. Recycling is still possible in the absence of Florisil, but the dropoff in activity appears greater. In the presence of SiO_2, the ee is 87%.

(45) If the reaction was stopped prior to completion, complete incorporation of MeOH was observed at the anomeric carbon of the dihydropyran and the equilibrium cis:trans ratio was 1:3.

Table 9. Catalyzed Hetero Diels−Alder Reactions with [Cu((*S*,*S*)-Bu-box)$(H_2O)_2$]$(OTf)_2$ (**27a**) and 3 Å Molecular Sieves (Eq 32)

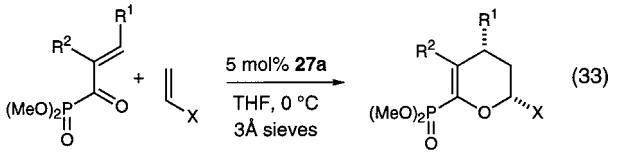


(32)

hetero diene	hetero dienophile	product (*endo/exo*)[a]	yield (%)	% ee[a]
				
		26a: R = Me[b] (24:1)	87	97
		26b: R = Ph[c] (>20:1)	93	97
		26c: R = ^{i}Pr[c] (22:1)	95	96
		26d: R = OMe[b] (59:1)	90	98
		26e: R = OEt[b] (55:1)	98	98
		26f: R = SBn[b] (>20:1)	97	99
				
		28b: R = Ph[b] (16:1)	96	97
		28c: R = ^{i}Pr[b] (16:1)	94	95
				
		29a: R = Et[b] (>20:1)	94	97
		29b: R = Ph[d] (>20:1)	91	99
				
		30a: R = Me[b] (64:1)	99	99
		30b: R = OMe[b] (10:1)	94	98

[a] Determined by capillary GC or chiral HPLC. [b] Absolute configuration assigned by analogy. [c] Absolute configuration assigned by chemical correlation to a compound of known absolute configuration (vide infra). [d] Reaction conducted with 5 mol % of **27a**.

Table 10. Hetero Diels−Alder Reactions of Acyl Phosphonates and Enol Ethers and Sulfides Catalyzed by [Cu((*S*,*S*)-Bu-box)$(H_2O)_2$]$(OTf)_2$ (**27a**) (Eq 33)

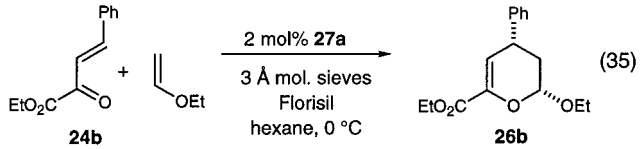


(33)

R^1	R^2	X	% yield	endo/exo	% ee[a]
Me	H	OEt	84	36:1	93 (93)
Ph	H	OEt	95	22:1	97 (94)
i-Pr	H	OEt	92	22:1	95 (93)
OEt	H	OEt	92	44:1	97 (93)
Me	Me	OEt	98	25:1	≥90 (≥94)
Me	H	SEt	75	16:1	96 (76)

[a] Numbers in parentheses refer to enantiomeric excesses obtained when the reaction was conducted with 10 mol % of Cu(*S*)-*t*-Bu-box)$(SbF_6)_2$ (**2a**), CH_2Cl_2, −78 °C.

Table 11. Catalyst Recycling in a Hetero Diels−Alder Reaction with an Apparently Insoluble Catalyst (Eq 35)



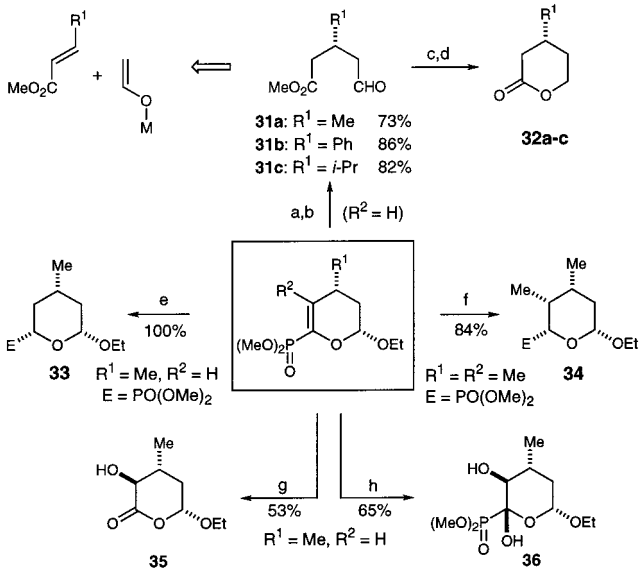
(35)

cycle[a]	time (h)	% yield	endo/exo	% ee
1	<1.0	89	>99:1	96
2	1.1	98	>99:1	96
3	1.5	91	>99:1	96
4	2.3	98	>99:1	93
5	4.0	92	>99:1	95

[a] See text.

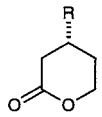
Other reactions that preserved the integrity of the cyclic ether were investigated. Diastereoselection was essentially complete in all manipulations of the enol double bond due to the influence exerted by the proximal stereogenic center (dr >20:1). Transition metal catalyzed reduction of the double bond introduced one or two additional stereogenic centers into the molecule, depending on the substrate. For the trisubstituted olefin, Pd/C was sufficient to effect catalytic hydrogenation (Scheme 2, step e, R^1 = Me, R^2 = H), but for the hindered tetrasubstituted enol ether (R^1 = R^2 = Me), Rh/C was the required catalyst (step f).

Scheme 2[a]



[a] Reaction conditions: (a) HCl/MeOH, reflux; (b) PPTS (cat.), acetone/H_2O (4:1), reflux; (c) $NaBH_4$, EtOH, 25 °C; (d) TFA, CH_2Cl_2, 25 °C; (e) H_2 (300 psi), Pd/C (cat.), EtOAc, 25 °C; (f) H_2 (550 psi), Rh/C (cat.), EtOAc, 25 °C; (g) 10 mol % OsO_4, NMO, ^{t}BuOH/H_2O (10:1); (h) $RuCl_3 \cdot (H_2O)_3$ (7 mol %); $NaIO_4$, CH_3CN/EtOAc/H_2O (3:3:1), 0 °C.

(46) R = Me (**32a**) and Ph (**32b**): (a) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556. R = *i*-Pr: (b) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199.



32a-c

R	$[\alpha]_D$ (config.)	lit.[46] $[\alpha]_D$ (config.)	solvent
Me (**32a**)	+19.1° (4*R*)	+7.0° (4*R*, 61% ee)	$CHCl_3$
Ph (**32b**)	–3.4° (4*R*)	+0.78° (4*S*, 21% ee)	$CHCl_3$
i-Pr (**32c**)	+24.6° (4*R*)	+26.6° (4*R*)	$CHCl_3$

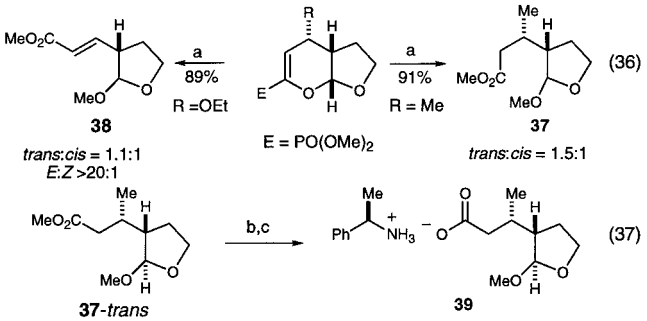
Oxidation of the enol bond was feasible: the α-hydroxy lactone **35** was obtained stereoselectively in 53% yield under standard dihydroxylation conditions (cat. OsO_4, NMO), presumably via the intermediacy of the α,*β*-dihydroxy phosphonate **36** (step g). Such a species was not observed spectroscopically (^{1}H NMR), but it was suspected that the equivalent of trialkylamine base generated during the course of the reaction was responsible for breakdown of the putative diol intermediate. Oxidation using the conditions of Shing,[48] which neither employ nor generate endogenous base, allowed for isolation of the diol **36**, mp 112−114 °C, again with high diastereoselection (step h). Subjection of **36** to the action of $NaHCO_3$ (MeOH, 25 °C, 5 min) resulted in elimination of dimethyl phosphite, generating the same lactone obtained under the OsO_4/NMO conditions (where MeOH had been incorporated at the anomeric carbon).

Bicyclic enol phosphonates were also amenable to synthetic manipulation. Catalytic amounts of $Sm(OTf)_3$ were sufficient to induce the same type of solvolysis reaction performed above (Scheme 3, step a). Good yields were obtained for the acetal esters **37** and **38**, products that might potentially serve as protected lactones. In the case of the alkoxy-substituted adduct, solvolysis further resulted in elimination of MeOH to stereoselectively give an α,*β*-unsaturated ester.

The anomers of the *β*-methyl-substituted ester **37** were separated by flash chromatography and the trans isomer was saponified. The solid ammonium carboxylate **39** was obtained after acidification and treatment with (*R*)-(+)-α-methylbenzylamine (steps b and c). Recrystallization gave the pure salt, mp 115−117 °C, in 75% yield for two steps and an X-ray crystal structure of the product established the configuration of the carboxylate's methyl-bearing stereogenic center.[49]

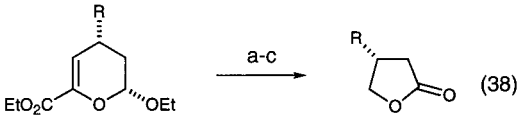
The absolute configurations of **26b** and **26c** were secured in the following manner (Scheme 4): ozonolysis of the enol double bond with reductive workup (O_3, CH_2Cl_2/MeOH, −78 °C; $NaBH_4$), hydrolysis of the resultant lactol ethyl ether (HCl, THF/H_2O, 65 °C), and lactol oxidation (TPAP, NMO, CH_2Cl_2, 25 °C) afforded lactones **40b** and **40c** in low yield. A comparison of optical rotations to those in the literature demonstrated that the sense of asymmetric induction was the same for cycloadditions of α-keto esters and acyl phosphonates catalyzed by bis(oxazoline) Cu(II) complexes.[50]

Scheme 3[a]



[a] Reaction conditions: (a) 5 mol % $Sm(OTf)_3$, MeOH, reflux; (b) LiOH, THF/H_2O, 25 °C; (c) *R*-(+)-α-methylbenzylamine, CH_2Cl_2, 25 °C

Scheme 4[a]



26b: R = Ph
26c: R = *i*-Pr

40b, 9%
40c, 11%

Product, R (config.)	$[\alpha]_D$ (*c*, solvent)	lit.[48] $[\alpha]_D$
40b, Ph (3*S*)	+38° (0.34, MeOH)	+51°
40c, *i*-Pr (3*S*)	-11° (0.52, $CHCl_3$)	+14.7° (3*R*)

[a] Reaction conditions: (a) O_3, CH_2Cl_2/MeOH, −78 °C; $NaBH_4$, 25 °C; (b) 1 M aq HCl/THF, 65 °C; (c) TPAP (cat.), NMO, 4 Å mol sieves, CH_2Cl_2, 25 °C.

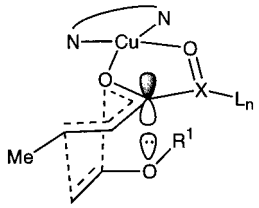


Figure 2. Secondary orbital interaction (dienophile(HOMO) → diene(LUMO)) for the endo transition structure.

Reaction Stereochemistry

Mechanistic studies on reactions of α,*β*-unsaturated carbonyls with alkyl enol ethers support a concerted asynchronous reaction pathway.[51] With regard to simple diastereoselection, the consistent preference for the cis-2,4-substituted dihydropyran products is consistent with an endo transition state. A secondary orbital interaction between the oxadiene C-2 (LUMO) and dienophile OR (HOMO) has been proposed as a stabilizing influence in these processes (Figure 2).[52] Houk has performed DFT calculations for the reaction of acrolein and methyl vinyl ether that support the experimental endo transition state preference.[53]

In addressing the subject of enantiofacial selectivity, we have noted that [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes **1a** and **2a** exhibit stereoregular behavior across a number of reaction families. For substrates that can engage in bidentate coordination to the chiral Lewis acid, there is evidence supporting a reaction pathway proceeding via a distorted square-planar Cu(II)·substrate com-

(47) By verifying the absolute configuration of **7a**, it was possible to chemically correlate cycloadducts **10**, **11**-*endo*, and **11**-*exo*. Lewis acid-catalyzed alcohol exchange ($Sm(OTf)_3$, EtOH) at the anomeric carbon for **10**, **12**-*endo*, and **12**-*exo* generated compound **7a** as a cis/trans mixture. Comparison of retention times by GC and chiral HPLC (with co-injection of authentic samples) allowed stereochemical assignment. The correlations demonstrate that both heterodienophiles approach **6a** from the same enantioface in the endo transition state. The configuration at the methyl-bearing stereocenter is opposite for the exo product derived from *tert*-butyl vinyl ether (**12**-*exo*). For further details, see the Supporting Information.

(48) (a) Shing, T. K. M.; Tai, V. M. F.; Tan, E. K. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2312. (b) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W. F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.

(49) See the Supporting Information. The authors thank Mr. Kevin R. Campos for solving this crystal structure.

(50) **40b**: (a) Helmchen, G.; Nill, G. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 66. **40c**: (b) King, C.-H. R.; Poulter, C. D. *J. Am. Chem. Soc.* **1982**, *104*, 1413.

(51) Desimoni, G.; Bamba, A.; Monticelli, M.; Nicola, M.; Tacconi, G. *J. Am. Chem. Soc.* **1976**, *98*, 2947.

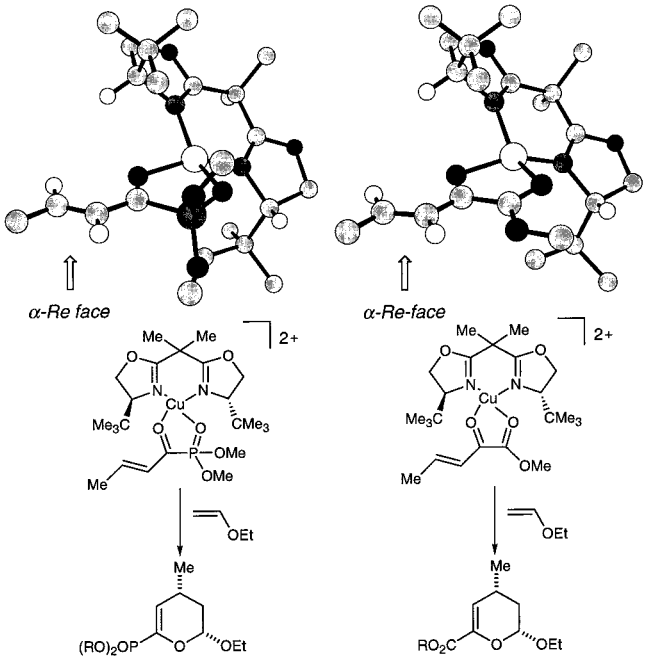
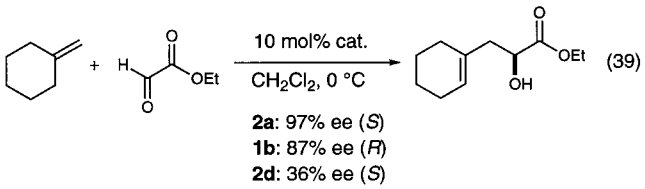


Figure 3. Calcualted PM3 structures of [Cu(*t*-Bu-box)(**6a**)]$^{2+}$ and [Cu(*t*-Bu-box)(keto ester)]$^{2+}$.

plex. X-ray crystallography, double stereodifferentiating reactions, PM3 semiempirical calculations, and EPR spectroscopy have supported the viability of such an intermediate.[54] Further, the enantiofacial bias exerted by **1a** and **2a** is rigidly consistent in reactions of compounds that may participate in chelation: *N*-acyl imides, glyoxylate and pyruvate esters, acyl phosphonates, α-keto esters, and alkylidene malonates. The results of semiempirical calculations (PM3) for catalyst·substrate complexes illustrated in Figure 3 suggest that the analysis described above may be reasonably extended to the cycloaddition chemistry detailed herein.[55]

In contrast, the mechanistic details of employing [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes **1b** or **2b** in these reactions had not been scrutinized. The first report of a *t*-Bu/Ph enantioselectivity reversal was made by Jørgensen and Johannsen in their studies of normal demand hetero Diels−Alder reactions between glyoxylate esters and dienes.[56] In a series of publications, the authors proposed that a tetrahedral copper center was responsible for the turnover in absolute stereochemistry; the configuration of the product was the support provided for this hypothesis. Our results in the inverse electron demand hetero Diels−Alder reaction and analogous observations in catalysis of the glyoxylate ene reaction (eq 39),[57] coupled with the dearth of structural and mechanistic information on this phenomenon, warranted a more detailed investigation.[58]



2a: 97% ee (*S*)
1b: 87% ee (*R*)
2d: 36% ee (*S*)

Catalyst Structure. With the goal of understanding the coordination chemistry of the Cu(II) center in complexes **2a**−**c**, an X-ray crystallographic study of the hydrated derivatives of those complexes was undertaken. Crystals of the derived bis(aquo) complexes **41a**−**c** were obtained upon exposure of dichloromethane solutions of **2a**−**c** to atmospheric moisture.[59] The structural details of those complexes revealed an interesting trend that is relevant to the experimental results summarized above (Figure 4). In *tert*-butyl-substituted bis(aquo) complex **41a**, the Cu(II) center was characterized by a distorted square-planar geometry. The distortion of the ligated water molecules was away from the oxazoline substituents an average of +33.3°. The water ligands of the analogous isopropyl-substituted bis(aquo) complex **41c** displayed a similar distortion from square planarity, but the magnitude of the tilt was significantly smaller: an average of +7.0°. This change suggested that the origin of distortion observed for **41a** was steric, not electronic, in nature. Such effects are well-precedented in the chemistry of copper(II).[60] Finally, phenyl-substituted bis(aquo) complex **41b** also exhibited noticeable distortion from square planarity; however, in that case the water molecules tilted *toward* the oxazoline substituents an average of −9.3°.[61]

If the bidentate substrates undergoing activation adopt distortions that resemble those observed in the X-ray structures, substantial differences in the local environment of the two prochiral faces might be expected. The enantioselectivity trends for both the glyoxylate ene and hetero Diels−Alder reaction placed [Cu((*S*,*S*)-*i*-Pr-box)](X)$_2$ complexes in the middle of the spectrum, between the [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ and [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes. As evidenced by Figure 4, the structural distortion for the isopropyl complex was also intermediate to that exhibited by the phenyl or *tert*-butyl-derived complexes. While it has not been possible to establish a causal link between these two phenomena, the fact that the two trends mirror each other is nonetheless interesting.

Mechanistic Studies. While we have provided calculated structures of putative intermediates, we recognized the need to consider not only the nature of the catalyst−substrate complexes but interactions between that binary complex and the other reacting partner. To facilitate this analysis, we considered in the extreme two possible transition structures that differ in metal center geometry (Figure 5). A change in geometry at copper from square planar to tetrahedral was expected to expose the

(52) For a summary, see: Boger, D. l. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 451−512.

(53) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064.

(54) X-ray crystallography: (a) Reference 19b. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 1994. Double stereodifferentiating experiments: (c) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. PM3 and EPR experiments: (d) Reference 9.

(55) Geometry optimizations were performed at the PM3(tm) level using the Spartan Semiempirical Program 5.0 (Wavefunction Inc., Irvine, CA 92612) on a Silicon Graphics Impact 10000 (195 MHz, 128 M RAM) running IRIX 6.2. Calculations were performed without counterions or solvent using these parameters: optcycle = 5000, maxcycle = 10000, charge = 2, multiplicity = 2. Calculations converged (energy difference between cycles <0.0005 kcal/mol) in ≤4 h CPU time.

(56) (a) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (b) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321. (c) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169. (d) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117. (e) Yao, S. L.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. (f) Reference 11.

(57) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(58) Other examples of an enantioselectivity turnover from *t*-Bu to Ph bis(oxazoline): (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165. (b) Sibi, M. P.; Ji, J.; Wu, J. H.; Guertler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200−9201. (c) Yao, S.; Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2345.

(59) The authors thank David M. Barnes (**41a**) and Dr. Christopher S. Burgey (**41b,c**) for obtaining these crystals and Mr. Kevin R. Campos for solving the structures.

(60) Hathaway, B. J.; Billing, D. E. *Coord. Chem. Rev.* **1970**, *5*, 143.

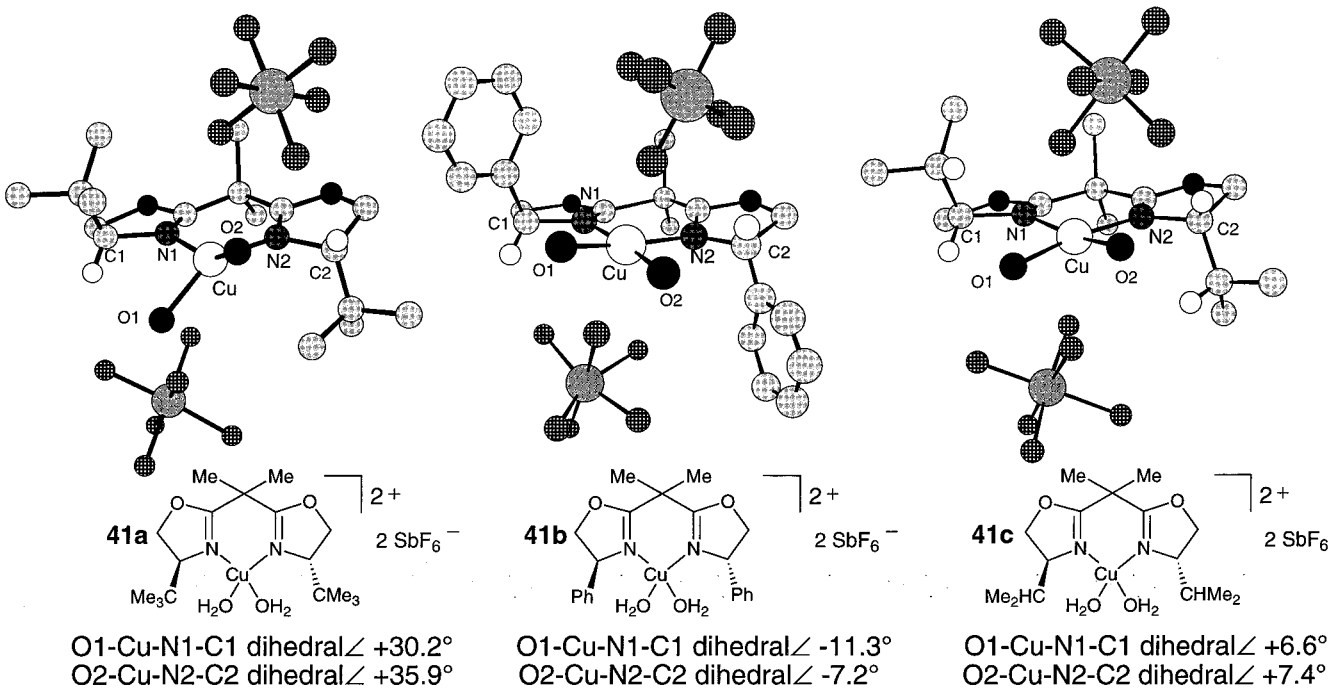


Figure 4. X-ray crystal structures of [Cu(*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**41a**), [Cu(Ph-box) $(H_2O)_2$]$(SbF_6)_2$ (**41b**), and [Cu(*i*-Pr-box)$(H_2O)_2$]$(SbF_6)_2$ (**41c**) with selected bond angles.

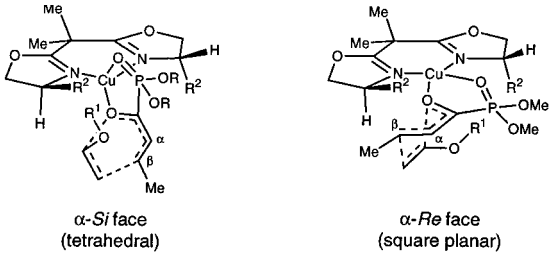


Figure 5. Tetrahedral and square planar transition structures for hetero Diels−Alder reactions of acyl phosphonates with enol ethers.

opposite enantioface for reaction, by virtue of the altered spatial relationship between the pendant oxazoline substituent (R^2) and the heterodienophile π-system.[62]

The finding that **2b**-catalyzed cycloadditions of crotonyl phosphonate **6a** and methyl, ethyl, and *tert*-butyl vinyl ethers were all highly endo selective was of particular interest to us. Houk and co-workers have found experimental and computational evidence that indicated a preferred *s*-trans enol ether conformation in the transition state of inverse electron demand hetero Diels−Alder reactions.[53] In the *s*-trans conformation, severe steric interactions between the approaching heterodienophile and activated catalyst−substrate complex would be expected if the copper(II) center was tetrahedral ($R^1 \leftrightarrow R^2$). The absence of such a steric effect, as evidenced by the uniformly high diastereoselectivities, argued against a change to tetrahedral geometry.[63] Application of the same test to the glyoxylate ene reaction is also instructive, since **1b** is a highly endo selective catalyst with the sterically demanding cyclohexene (endo:exo 95:5, 94% ee).

The manifestation of nonlinear effects in asymmetric catalysis can have important consequences for the elucidation of reaction mechanism.[64] The enantiomeric excess of the adduct dihydropyran for the hetero Diels−Alder reaction between acyl phosphonate **6c** and ethyl vinyl ether was monitored as a function of enantiomeric composition of the catalyst (Figure 6). A linear relationship between the enantiomeric excess of the catalyst and that of the product was observed, thereby suggesting that neither catalyst aggregation nor dimer formation was present. Nonlinear effects were similarly absent in the catalyzed glyoxylate ene reaction; however, the successful isolation of crystals of Cu-((*S*,*S*)-Ph-box)$_2$(OTf)$_2$ demonstrated that catalyst sequestration by way of 2:1 ligand−metal complexation was feasible, but not kinetically significant under the reaction conditions.[65] The lack of nonlinear effects in this investigation contrasted with other systems employing divalent transition metal bis(oxazoline) and bis(imine) complexes in which substantial asymmetric amplification was reported.[66]

Considering the significant role that electronic effects can play in asymmetric reactions,[67] substituted phenyl−bis(oxazoline) ligands of varying electronic character were synthesized and evaluated in catalytic hetero Diels−Alder reactions (Table 12).[68] While no significant differences in enantioselectivity were observed for ligands with electron-poor or -rich aryl moieties, the contribution of the electronic effects was not discounted. Ample precedent exists for enantioselective processes in which

(61) (a) We have considered two plausible sources for this distortion: electrostatic effects and hydrogen bonding. For hydrogen bonding of water with benzene, see: Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W. A.; Blake, G. A. *Science* **1992**, *257*, 942. In that case the separation of the center of mass (C_6H_6−H_2O) was 3.32 Å; the distance from the water oxygen to the phenyl centroid is ca. 3.9 Å for **41b**. (b) Attempts to model this structure at the PM3 level (omitting the SbF_6 counterions) successfully reproduced the direction of distortion, but not the magnitude (ca. 30°).

(62) For experimental verification of this effect in Diels−Alder reactions of Cu(II) vs Zn(II) Lewis acids, see: Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481.

(63) The above discussion relies on reactions proceeding through a concerted, asynchronous transition state, but at this time it is not possible to exclude a two-step mechanism. Tietze and Evans have both provided experimental evidence for concerted cycloadditions: (a) Tietze, L. F.; Bratz, M.; Machinek, R.; Kiedrowski, G. v. *J. Org. Chem.* **1987**, *52*, 1638. (b) Reference 11a. Even if the reaction occurs in two steps, the uniformly high diastereoselectivities suggest a highly ordered transition state.

(64) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2923.

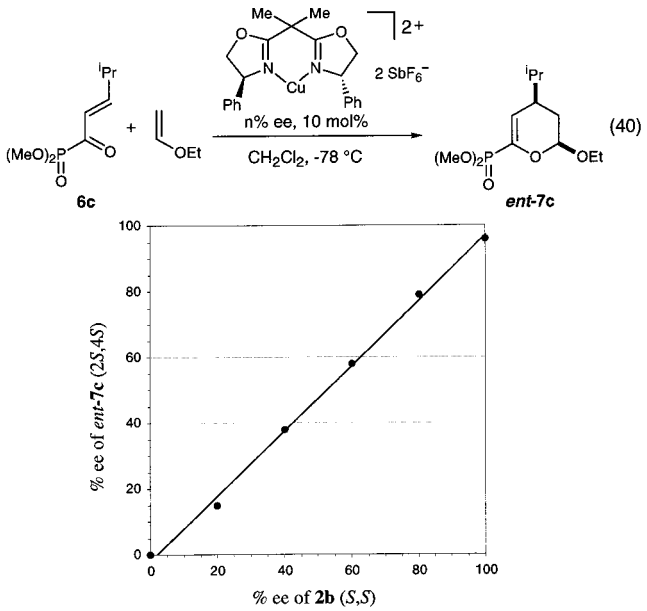
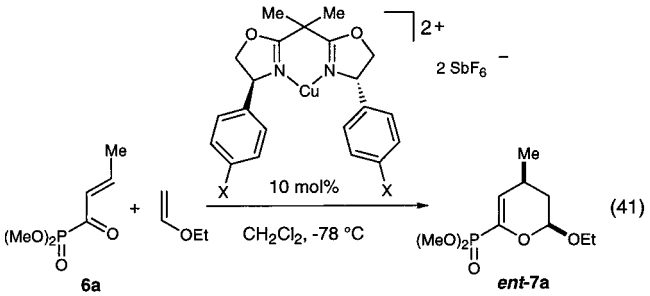


Figure 6. Study of nonlinear effects in hetero Diels−Alder reactions employing catalyst **2b**.

Table 12. Electronic Effect of Phenyl Bis(oxazoline) Ligand in the Catalyzed Hetero Diels−Alder Reaction (Eq 41)



entry	X	% ee
1	Cl	89
2	H	93
3	OMe	93

dipole−dipole and van der Waals attractions are implicated, but unaffected by pertubations in the π-donor capability of the phenyl group.[69]

As indicated previously, Cu(box) complexes exhibited a favorable temperature−enantioselectivity profile for catalytic hetero Diels−Alder reactions of acyl phosphonates and keto esters, an observation with consequences for the understanding of the stereochemical outcome of these reactions. Eyring plots for cycloadditions conducted with **1a** and **1b** (Figure 7) both showed a linear dependence of ln(% major enantiomer/% minor enantiomer) versus reciprocal temperature, demonstrating that only two diastereomeric transition states were responsible for the observed enantiomer ratios.[70] Consequently, competing metal geometries were effectively excluded.

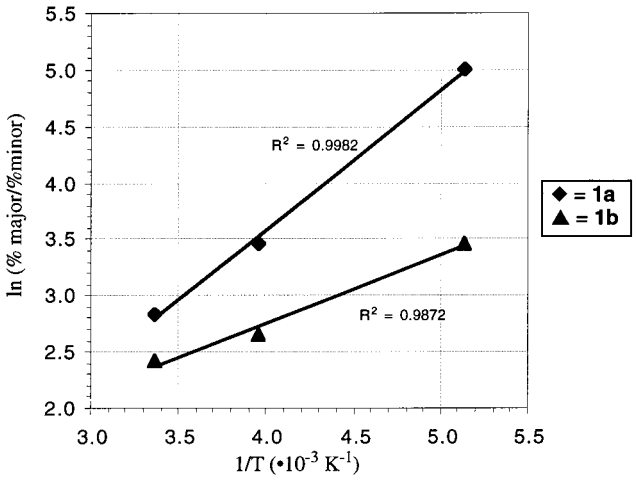


Figure 7. Eyring plots for the hetero Diels−Alder reaction of **6a** and ethyl vinyl ether catalyzed by [Cu(*t*-Bu-box)](OTf)$_2$ (**1a**) and [Cu(Ph-box)](OTf)$_2$ (**1b**).

In our previous studies of carbocyclic Diels−Alder and pyruvate aldol reactions catalyzed by Cu(box) complexes, mechanistic evidence pointed to the intermediacy of a square-planar catalyst·substrate complex that was responsible for the observed enantioselection. In both of those reactions, and now with the hetero Diels−Alder reaction catalyzed by **1a** and **1b**, Arrhenius behavior was observed, implying a strong resistance of the metal center to geometric deformation (i.e., square-planar → tetrahedral interconversion). In contrast, the Cu(pybox)-catalyzed aldol reaction, while highly enantioselective at −78 °C, did not exhibit Arrhenius behavior. A low energetic barrier for the interconversion of square-pyramidal and trigonal-bipyramidal geometries was postulated as the source of the poor temperature−enantioselectivity profile. The implication of these results is clear: if the enantioselectivity turnover in the hetero Diels−Alder reaction is a consequence of a new metal center geometry, that geometry must react to the complete exclusion of all others over a 100 °C temperature range. Such a scenario appears unlikely considering the X-ray crystal structures **41a** and **41b** that indicated a *reduced* propensity of phenyl(box) copper complexes to distort from square planarity relative to their *tert*-butyl counterparts. A similar conclusion was recently reached by Davies and Deeth in the course of their computational study of bis(oxazoline) Cu(II) complexes.[71]

If a square-planar catalys−substrate complex is operative in reactions mediated by **1b**, then approach of the dienophile must occur syn to the oxazoline substituent. While it is difficult to rationalize such an occurrence, a model that does fit the experimental evidence stipulates that the π surface of the phenyl ring is able to stabilize the partial positive charge that arises from the asynchronous transition state (Figure 8).[72] Such a transition structure is not possible for 1,1-disubstituted enol ethers such as α-trialkylsiloxystyrene due to the abutment of the enol ether substituent with the oxazoline phenyl ring: as noted previously, those heterodienophiles show the same facial selectivity using both *tert*-butyl and phenyl bis(oxazoline) catalysts.[73] This proposal should be construed as speculative;

(65) Barnes, D. M. Ph.D. Thesis, Harvard University, 1997.

(66) (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (b) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074. (c) 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.

(67) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

(68) The ligands were synthesized according to the method of ref 19b. For synthessis of the amino alcohols, see: (a) Chang, H. T.; Sharpless, K. B. *Tetrahedron Lett.* **1996**, *37*, 3219. (b) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.

(69) (a) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802. (b) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184. (c) Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156.

(70) Buschmann, H.; Scharf, H.-D.; Hoffmann, H.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

(71) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233.

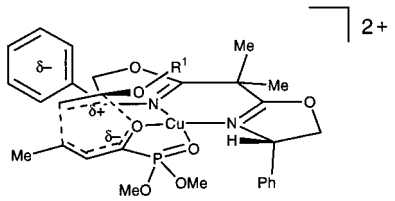


Figure 8. Proposed π-stabilization of an asynchronous hetero Diels−Alder transition state.

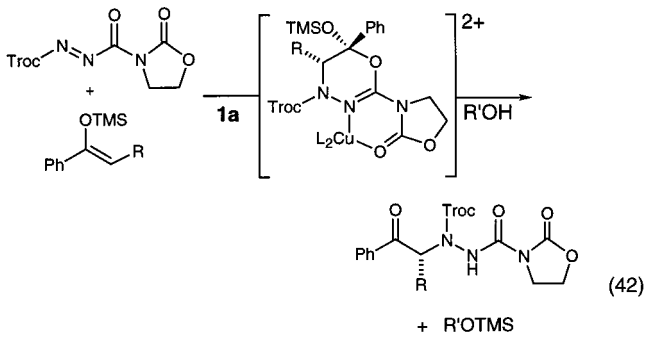
however, the accumulated experimental evidence provides more support for it than for a tetrahedral copper intermediate.

Conclusions

The asymmetric hetero Diels−Alder reaction of α,β-unsaturated carbonyls with electron-rich alkenes catalyzed by C_2-symmetric bis(oxazoline) Cu(II) complexes provides an expedient entry into enantioenriched dihydropyrans. A number of α,β-unsaturated acyl phosphonates and β,γ-unsaturated α-keto esters and amides have been successfully employed as heterodienes, while enol ethers and sulfides and certain ketone silyl enol ethers have functioned well as heterodienophiles. Of particular note is the development of a simple reaction protocol that employs a solid air-stable catalyst, low catalyst loadings, and convenient reaction temperatures, conditions that render these reactions particularly attractive from a preparative standpoint.

The derived cycloadducts may be transformed to useful chiral building blocks. Under acidic conditions, desymmetrized glutaric acid derivatives are obtained, while oxidation or reduction leaves the heterocycle intact and delivers highly functionalized tetrahydropyran products. The absolute configurations were determined for nine cycloadducts by chemical or crystallographic methods; the stereochemical outcome for all reactions catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes **1a** and **2a** is consistent with the intervention of a distorted square-planar catalyst−substrate complex. Structural and mechanistic studies have been employed to study the source of asymmetric induction for reactions catalyzed by [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes **1b** and **2b**; no evidence has been found to support the intervention of a tetrahedral copper species in reactions catalyzed by phenyl bis(oxazoline) copper(II) complexes.

The high diastereoselectivity for catalyzed hetero Diels−Alder reactions is a result of frontier orbital control and/or electrostatic effects that preferentially place the OR substituent in proximity with the heterodiene carbonyl carbon (endo orientation). This stereocontrol element has been implicated in related conjugate addition reactions to unsaturated imides and azaimides. Our collective experimental observations suggest that enol amination reactions (eq 42),[74] Mukaiyama Michael reactions (eq 43),[73]



(42)

and hetero Diels−Alder reactions are mechanistically related;

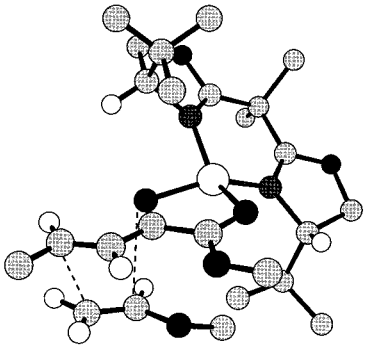
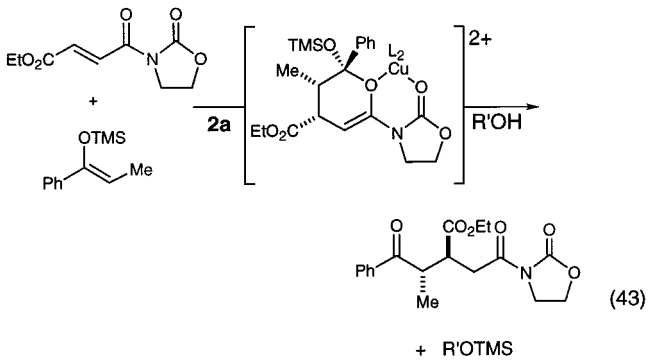


Figure 9. Qualitative model of the hetero Diels−Alder transition state showing stereochemical relationships between reactants.

the diastereoselectivity for all these processes can be accounted for by an endo transition structure (Figure 9).



(43)

This investigation has attempted to provide some evidence to support the notion that cycloadditions catalyzed by chiral copper complexes may be employed to efficiently and selectively assemble heterocycles. It is hoped that the reactions detailed herein will be of some use in the enantioselective construction of pyran rings, prevalent structural units in organic chemistry.

Acknowledgment. Support for this research was provided by the NSF. Graduate fellowships from the NSF (J.S.J. and E.J.O.), Pharmacia and Upjohn (J.S.J.), and Roche (J.S.J.) are gratefully acknowledged. The NIH BRS Shared Instrumentation Grant Program 1-S10-RR04870 and the NSF (CHE 88-14019) are acknowledged for providing NMR facilities. The amino alcohols and acids utilized in the preparation of the box ligands were generously provided by NSC Technologies.

Supporting Information Available: Complete experimental procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992175I

(72) For an excellent discussion on cation π interactions, see: Dougherty, D. A. *Science* **1996**, *271*, 163.

(73) Since experiments suggest that reactions with α-trialkylsiloxystyrene are not concerted, antiperiplanar approach of the nucleophile should also be considered; however, reactions with *E* and *Z* propionate silyl enol ethers and ketene acetals in the study of the Mukaiyama Michael reaction have provided some evidence that these additions proceed via a synclinal transition state. Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865.

(74) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.