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ARTICLES

Chiral Bis(oxazoline) Copper(II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael, and Carbonyl Ene Reactions

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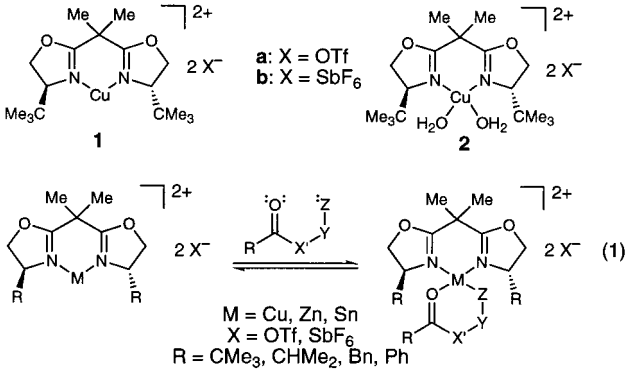
ABSTRACT

A bis(oxazoline) (box) copper(II) complex and its hydrated counterpart (**1** and **2**) function as enantioselective Lewis acid catalysts for carbocyclic and hetero Diels−Alder, aldol, Michael, ene, and amination reactions with substrates capable of chelation through six- and five-membered rings. X-ray crystallography of the chiral complexes reveals a propensity for the formation of distorted square planar or square pyramidal geometries. The sense of asymmetric induction is identical for all the processes catalyzed by [Cu((*S,S*)-*t*-Bu-box)](X)$_2$ complexes **1** and **2** (X = OTf and SbF) resulting from the intervention of a distorted square planar catalyst-substrate binary complex. These catalyzed processes exhibit excellent temperature−selectivity profiles. Reactions catalyzed by [Cu(*S,S*-Ph-pybox)](SbF$_6$)$_2$ and their derived chelation complexes are also discussed.

Many carbon−carbon bond-forming reactions employed in organic synthesis are subject to Lewis acid-promoted rate acceleration.[1] Cycloadditions, conjugate additions, and aldol additions are examples of important processes that strongly respond to Lewis acid activation. When the Lewis acid complex is chiral, the absolute stereochemical course of these catalyzed processes may be strongly influenced. The "Holy Grail" in this area of research has been a chiral Lewis acid that exhibits broad generality for asymmetric catalysis in more than one reaction family. Since the demands of each reaction are quite varied, the realization of this goal may not even be attainable.

In attempting to design general chiral Lewis acidic metal complexes, we have presumed that good levels of stereocontrol might be feasible, regardless of the reaction, if nominally similar substrates are activated in the same manner. In the pursuit of this plan, our laboratory has discovered that C_2-symmetric bis(oxazoline) (box) Cu(II) complexes **1** and their hydrated counterparts **2** are effective promoters of enantioselective Diels−Alder, aldol, ene, Michael, and amination reactions. The general design plan illustrated in eq 1 highlights the unifying feature of these studies: the substrates undergoing activation must be capable of chelating to the chiral Lewis acidic Cu(II) complex. Some of the catalyst−substrate complexes relevant to this review are illustrated in Figure 1. While we have successfully implemented this strategy with Zn(II)[2] and Sn(II)[3] Lewis acids, the majority of our work has focused on Cu(II). It is important to note the significant contributions of others in this area of research, especially the seminal contributions of Pfaltz and co-workers in the development of semicorrin complexes.[4]



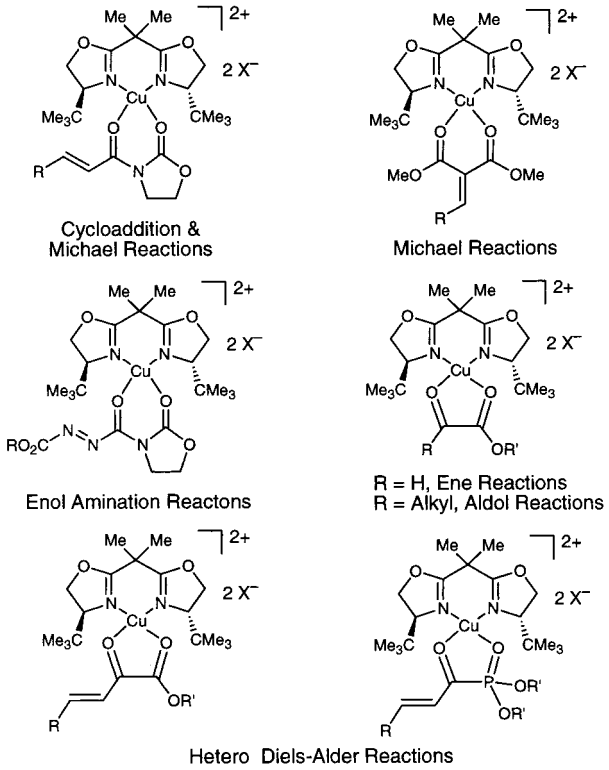


FIGURE 1. Representative catalyst−substrate complexes.

Rigidification of the reacting entity bearing chiral information is frequently achieved through hydrogen

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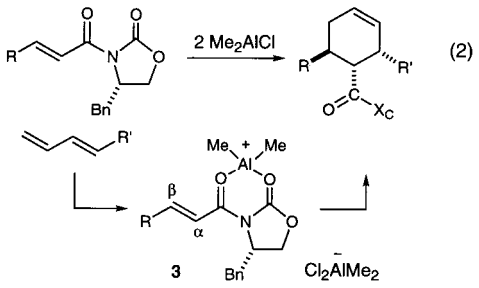
bonding, π-stacking, or chelation. In this context, some years ago our laboratory reported that chiral α,β-unsaturated acyl oxazolidinones undergo highly diastereoselective Me_2AlCl-promoted Diels–Alder reactions (eq 2).[5] Both

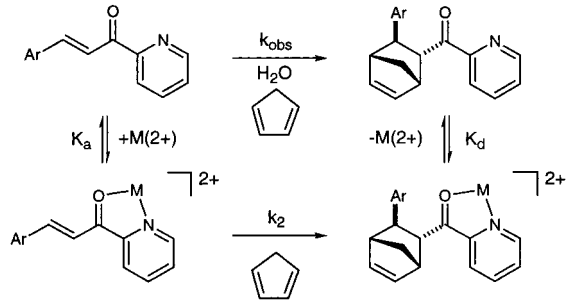


chelation control and π-stacking interactions have been identified as control elements in this process. The postulation of cationic chelated intermediate **3**, later observed spectroscopically by Castellino and Dwight,[6] correctly accounted for the observed stereoselectivity. As we have progressed to substoichiometric chiral controllers, we have continued to rely on chelation control to construct well-defined catalyst–substrate complexes. While one might argue that the chelation criterion in substrate selection is a limitation, this requirement enables catalyst applications among different families of reactions. This point is evident in the number of different processes that may be catalyzed with the chiral copper(II) complexes **1** and **2** with enantioselectivities regularly in excess of 90% (Figure 1). An important outcome of the chelation criterion is that the analysis of the catalyst–substrate complex usually leads to an unambiguous prediction of the sense of asymmetric induction.

Why Copper? Cu(II) functions effectively as a Lewis acidic center. The Irving–Williams order for divalent ions in the first transition series indicates that Cu(II) forms the most stable ligand–metal complexes (Mn < Fe < Co < Ni < **Cu** > Zn),[7] and dissociation of the chelating chiral ligand in derived complexes is apparently not a complication. In an apparent paradox, the exchange rate of $[Cu(H_2O)_6]^{2+}$ is also greater than those of other first row divalent transition metal ions, an effect consistent with labilization of axial ligands through Jahn–Teller distortion.[8] Cu(II) displays a propensity to form square planar or elongated tetragonal complexes.[9] For [Cu-box]$(X)_2$ complexes (X = weakly or noncoordinating ligand, e.g., OTf^- or SbF_6^-), coordination of a bidentate substrate is thus favored in the equatorial plane; Jahn–Teller distortion in the d^9 complex elongates the remaining apical sites where X may or may not reside. These considerations work in concert to provide well-defined complexes that exhibit excellent properties as catalysts. Engberts and coworkers have recently reported studies on divalent metal complexes as Diels–Alder catalysts in water.[10] The results of their experiments highlight the attractive attributes of Cu(II), an especially effective ion in both binding substrates and activating them for cycloaddition (Scheme 1).

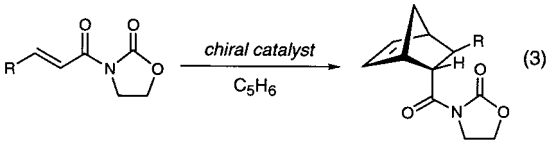
Carbocyclic Diels–Alder Reactions.[11] The pivotal reaction that provided the transition from auxiliary control (eq

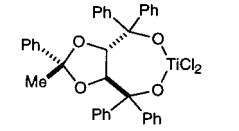
Scheme 1



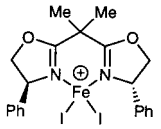
Irving-Williams Stability for M(2+): Mn < Fe < Co < Ni < **Cu** > Zn
K_a: Co < Ni < ***Cu*** > Zn
k_2: Co < Ni < ***Cu*** > Zn
k_{obs}: Co < Ni < ***Cu*** > Zn
endo/exo: Co ≈ Ni < ***Cu*** > Zn

2) to catalyst control was the imide Diels–Alder reaction illustrated below (eq 3). Narasaka's in-depth study on the

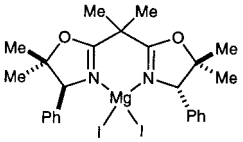




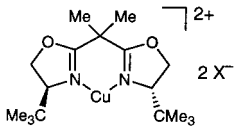
A (R = H, alkyl, aryl, CO_2R, $B(OR)_2$)



B (R = H)



C (R = H)



1a: X = OTf
1b: X = SbF_6

catalysis of this reaction with the chiral Ti(IV) catalyst **A**[12] documented the fact that effective absolute stereocontrol was possible. Subsequent studies by Corey et al. on the utility of the Fe(III) catalyst **B**,[13] and the Mg(II) analogue **C**,[14] indicated that other ligand–metal complexes might also serve as chiral catalysts; however, the viability of these latter complexes was restricted to unsubstituted dienophiles and low reaction temperatures. The objective of our investigation was to find the "best catalytic metal center" for this and related catalyzed processes. Our original work with bis(oxazoline) copper complexes focused on group transfer reactions, with studies of enantioselective cyclopropanation[15] and aziridination[16] reactions providing the foundation for the mechanistically distinct Lewis acid-catalyzed processes detailed in this Account. In 1993, we reported that [Cu(*S*,*S*)-*t*-Bu-box]$(OTf)_2$ complex **1a** was an effective chiral Lewis acid for the illustrated Diels–Alder reaction (eq 3).[17] Of the 10 metal triflates surveyed, Cu$(OTf)_2$ was uniquely effective in delivering cycloadductsin high diastereo- and enantiomeric excesses (−78 °C, >98% ee).[18,19]

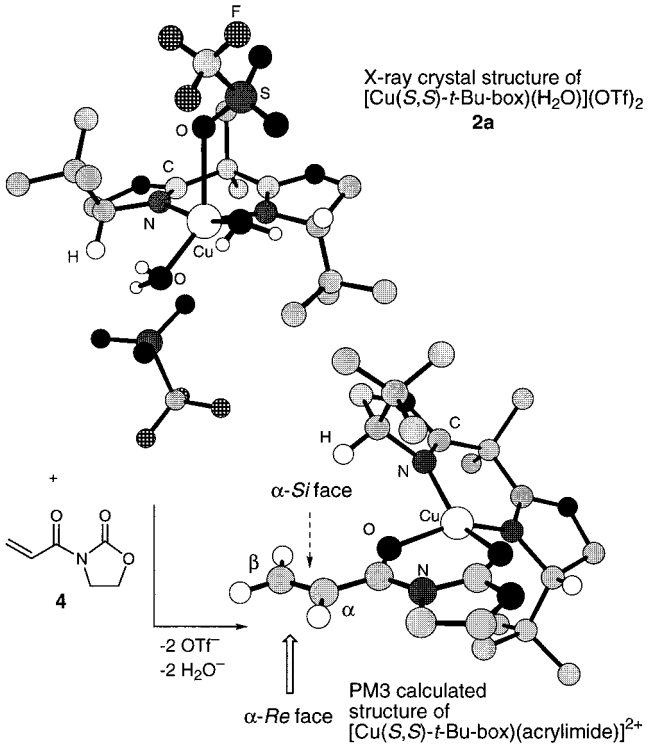


FIGURE 2. Stereochemical model for enantioselective cycloadditions.

The absolute configuration of the cycloadduct was consistent with bidentate dienophile activation by **1** in analogy to the previously discussed acyl oxazolidinone example (cf. **3**). An X-ray crystal structure of the hydrated complex [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$](OTf)$_2$ (**2a**) confirmed that the Cu(II) center was disposed in a distorted square pyramidal geometry with a weakly bound apical triflate ligand (Figure 2). A PM3 level semiempirical calculation of the presumed catalyst−substrate complex suggested a similar degree of distortion for the bound dienophile. A marked difference in the steric environment about the two prochiral π-faces was noted, consistent with the high level of observed enantioselection (>98%). The question of whether the solution geometry reflected that of the solid state was addressed by double stereodifferentiating experiments employing chiral imide dienophiles whose participation in diastereoselective Diels−Alder reactions has been documented.[17,18] Unambiguous matched and mismatched catalyst−substrate pairs were obtained that strongly support the square planar hypothesis. This is the most compelling experimental evidence to date for the square planar model and has provided the basis for explaining the *completely stereoregular behavior of the [Cu-((S,S)-t-Bu-box)](X)$_2$ complex in reactions of dicarbonyl substrates.*

Additional information regarding the impact of ligand structure and counterion on metal complex architecture was subsequently obtained from an X-ray crystallographic study of the hydrated *tert*-butyl-, isopropyl-, and phenyl-substituted bis(oxazoline)complexes (Figure 3).[20] In contrast to the hydrated triflate complex (**2a**, Figure 2), the SbF_6^- counterions are fully dissociated from the Cu(II) center in the *tert*-butyl-substituted bis(aquo) complex **2b**. As with **2a**, the Cu(II) center of **2b** is characterized by a distorted square planar geometry. The average distortion of the ligated water molecules away from the oxazoline substituents is +33.3°. The water ligands of the analogous isopropyl-substituted bis(aquo) complex **5** display a significantly smaller tilt from square planarity, an average of +7.0°. This change suggests that the origin of distortion observed for **2b** is steric, not electronic, in nature. Such

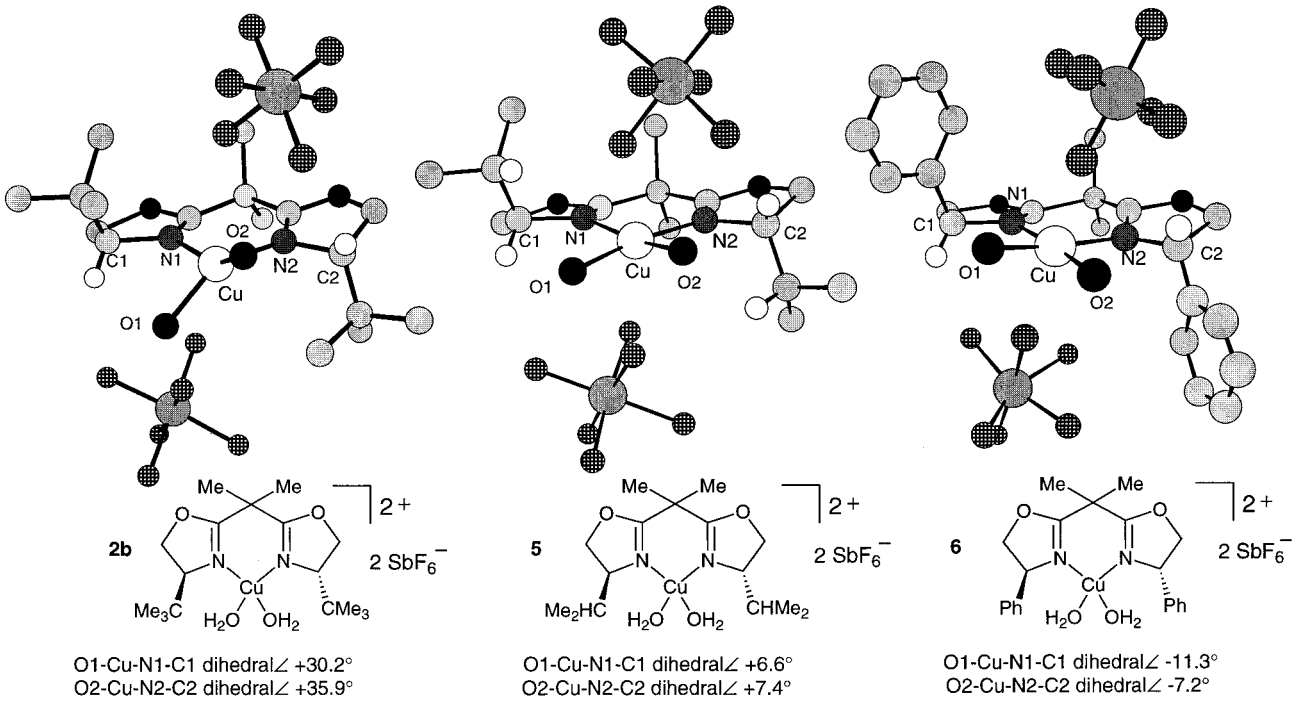


FIGURE 3. X-ray crystal structures of Cu[bis(oxazoline)$(H_2O)_2$]$(SbF_6)_2$ complexes.

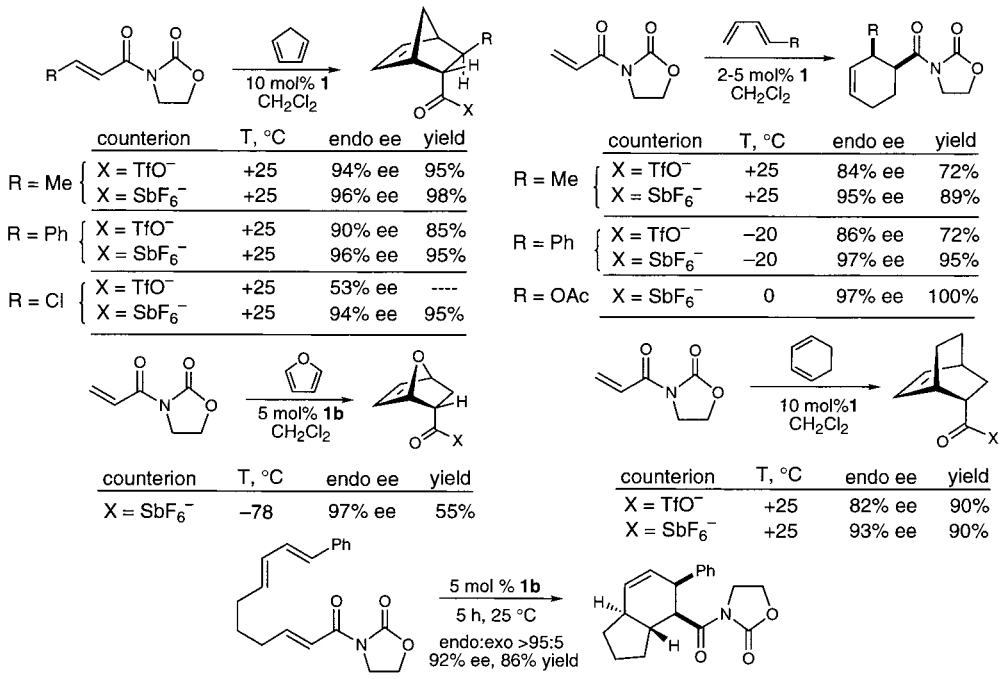


FIGURE 4. Diels–Alder reactions catalyzed by [Cu((*S,S*)-*t*-Bu-box)](X)$_2$ (**1a**, X = OTf and **1b**, X = SbF_6).

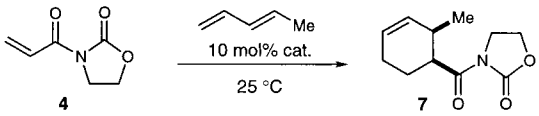
effects are well-precedented in the chemistry of copper(II).[9] Finally, phenyl-substituted bis(aquo) complex **6** also exhibits noticeable distortion from square planarity; however, in this case, the water molecules tilt *toward* the oxazoline substituents an average of −9.3°. The origin of this distortion has yet to be adequately explained but could be the result of electrostatic effects or a Ph−H_2O hydrogen bond.[21]

We have documented that the role of counterion in these copper complexes is significant for both catalyst activity and reaction enantioselectivity.[22] The SbF_6-derived complex **1b** is 20 times more reactive than its triflate (OTf)-derived counterpart **1a** in the Diels–Alder reaction. This discovery resulted in significant improvements in the scope of the reaction (Figure 4).[23]

In addition to the diene/dienophile pairs shown above, we have employed 1-acetoxy-3-methylbutadiene for an enantioselective synthesis of *ent*-Δ^1-tetrahydrocannabinol[24] and an intramolecular Diels–Alder reaction for the synthesis of (−)-isopulo'upone.[25] The furan–imide adduct was utilized in an asymmetric synthesis of *ent*-shikimic acid.[26]

Anhydrous vs Aquo Complexes. The crystalline aquo complexes [Cu((*S,S*)-*tert*-Bu-box)$(H_2O)_2$](OTf)$_2$ (**2a**) and [Cu((*S,S*)-*tert*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**2b**) have also been evaluated as Lewis acid catalysts in the illustrated reaction with piperylene (Table 1).[18] These data indicate that hydration of the triflate complex (**1a** → **2a**) effectively terminates catalysis; in contrast, the hydrated SbF_6 complex **2b** is nearly as active as its anhydro counterpart **1b**. Bench-stable **2b** is the catalyst of choice in many instances. Molecular sieves may be employed to reactivate the triflate complex (**2a** → **1a**); however, this protocol appears to inactivate the SbF_6 derivative **2b**.

Table 1. Diels–Alder Reactions of Imide 4 with Piperylene Catalyzed by [Cu(*t*-Bu-box)$(H_2O)_n$](X)$_2$ Complexes (Eq 4)[a]



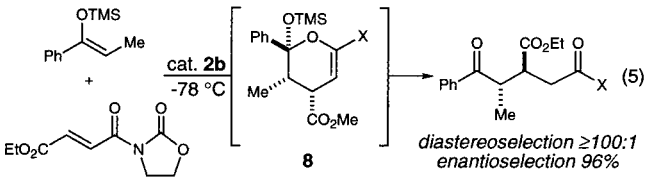
(4)

complex	time	conv (%)	ee, **7** (%)
[Cu(*t*-Bu-box)](OTf)$_2$ (**1a**)	15 h	94	84
[Cu(*t*-Bu-box)]$(SbF_6)_2$ (**1b**)	50 min	100	95
[Cu(*t*-Bu-box)$(H_2O)_2$](OTf)$_2$ (**2a**)	24 h	<10	–
[Cu(*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ (**2b**)	70 min	100	94

Since our initial reports, a number of publications on the use of bis(oxazoline) Cu(II) Lewis acids in enantioselective Diels–Alder reactions have appeared, most notably from Davies et al.[27] and Ghosh et al.[28] In addition, other chiral metal complexes have also been reported to catalyze this process; however, the substrate scope is typically not as broad as that with Cu(II) Lewis acids **1** and **2**.[11,19]

Our observations on ligand architecture, counterion, and solvent effects in the Diels–Alder reaction have provided useful information that has allowed us to extrapolate to the enantioselective catalysis of other processes.

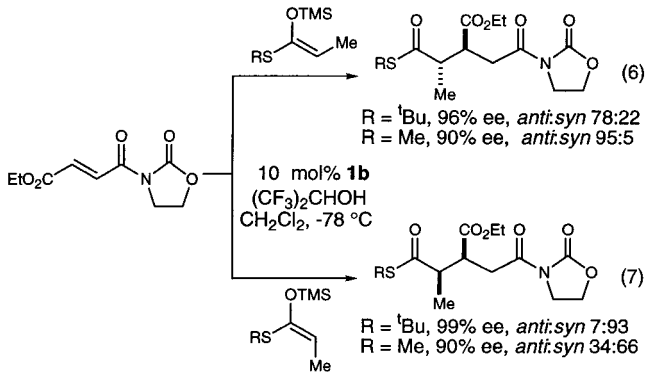
Michael Additions. The conjugate addition of latent carbon nucleophiles to Lewis acid-activated unsaturated carbonyls, the Mukaiyama Michael reaction, is mechanistically more complex than the Diels–Alder reaction due to issues of silicon transfer and the buildup of intermediates potentially poisonous to the catalyst. [Cu((*S,S*)-*t*-Bu-box)]$(SbF_6)_2$ complex **1b** catalyzed the enantioselective addition of enolsilanes to a fumaroyl imide, but only sluggishly and sometimes with incomplete conversion (eq 5).[29] In situ IR spectroscopy revealed an intermediate-whose appearance coincided with a loss of catalyst

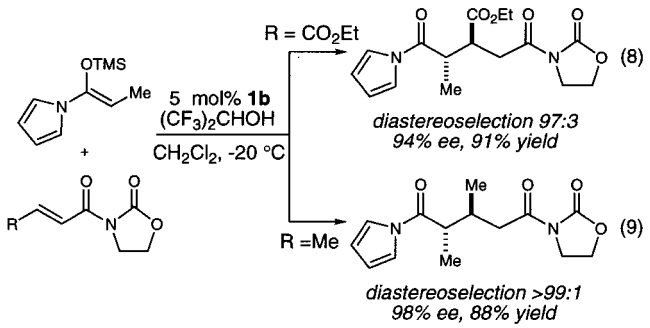


additive	yield	time
none	95%	4 d
$(CF_3)_2CHOH$	94%	3 h

activity. The intermediate could be isolated, and the structure was determined to be the formal hetero Diels–Alder adduct **8**. Dihydropyran **8** was readily decomposed with protic additives. Hexafluoro-2-propanol (HFIP) was generally most effective in this capacity, greatly accelerating the reactions and serving as the ultimate R_3Si^+ acceptor. Importantly, the alcohol additive did not affect the reaction selectivity, indicating that it functions solely in the turnover step. The premise that the Lewis basic urethane subunit is a competitive inhibitor was supported by experiments in which *N*-methyl 2-oxazolidone (1 equiv) was found to inhibit turnover, despite the presence of HFIP.

The scope of the addition reaction has been defined to include a number of substituted enolsilane nucleophiles. The reaction diastereoselectivity correlates with the geometry of the nucleophile: (*E*) silylketene thioacetals preferentially deliver *anti* adducts (eq 6), while (*Z*) silylketene thioacetals afford *syn* products (eq 7). Judicious selection of the *S*-alkyl group facilitates good diastereocontrol.

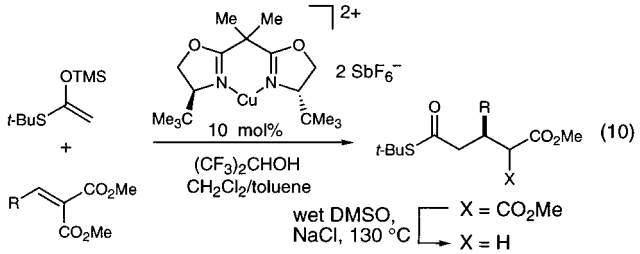




Enantioselective additions of silyl ketene aminals to less electrophilic Michael acceptors were also possible (eq 9). The absolute configuration of adducts derived from catalytic Michael reactions was consistent in all cases with the distorted square planar model described for the Diels–Alder reaction (Figure 2).

The beneficial effect of alcoholic additives has found use in several addition reactions we are studying. One example is the Mukaiyama Michael reaction of alkylidene malonates with silylketene thioacetals.[30] The [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$-catalyzed addition of acetate nucleophiles provided adducts with good efficiency and high levels of enantiocontrol for alkylidene malonates bearing sterically demanding substituents at the β-position (Table 2). The alkylidene malonate additions are complementary to the imide chemistry described above: the heightened electrophilicity of the Michael acceptor facilitates additions to extremely hindered alkenes. The adducts were easily transformed to desymmetrized glutaric acid derivatives under Krapcho decarboxylation conditions.[31]

Table 2. Catalyzed Michael Reactions of Alkylidene Malonates (Eq 10)



R	ee (%)	yield (%)	R	ee (%)	yield (%)
Ph	93	91	*c*-hex	95	99
2-furyl	94	88	*i*-Pr	93	93
2-naphthyl	93	90	*t*-Bu	90	89
2-MeOPh	99	92			

At the outset of the project, we were unsure if the bis(oxazoline) scaffold would provide the dissymmetry needed for an enantioselective reaction. In a strictly square planar copper complex, substrate complexation would place the reacting center on the ligand C_2 axis. Additionally, the prochiral center of the Cu(box)–alkylidene malonate complex would not reside near the ligand chirality, in contrast to the Cu(box)–imide complex. X-ray crystallographic analysis of the substrate (R = Ph) bound to the chiral catalyst simultaneously provided insight into the source of enantioselectivity and confirmed the hypothesis that dicarbonyl compounds coordinate to the copper center in a chelating fashion (Figure 5). The bound alkylidene malonate adopts a boat conformation with the copper atom at the apex. The distortion is such that the phenyl group is oriented away from the nearest oxazoline *tert*-butyl substituent and the aromatic ring is not coplanar with the alkylidene malonate π-system. The absolute stereochemical course of the reaction is consistent with nucleophilic attack on the less hindered convex surface of the catalyst–substrate complex.

Good enantiocontrol was realized in these additions only when the β-substituent was sterically demanding. We have speculated[30] that nonbonding interactions between the silylketene thioacetal and the β-substituent impose a nonvertical approach trajectory at an angle θ.[32] Such an

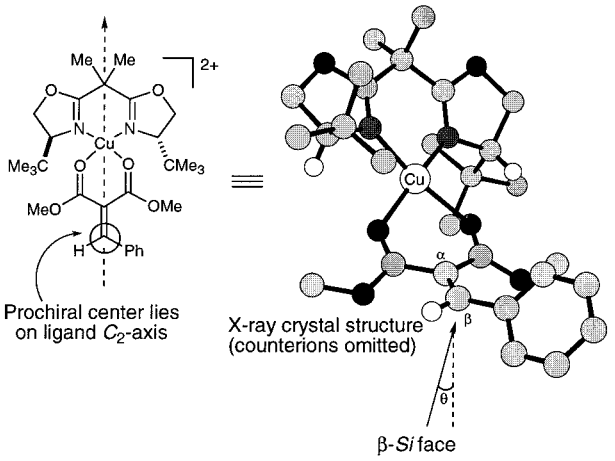
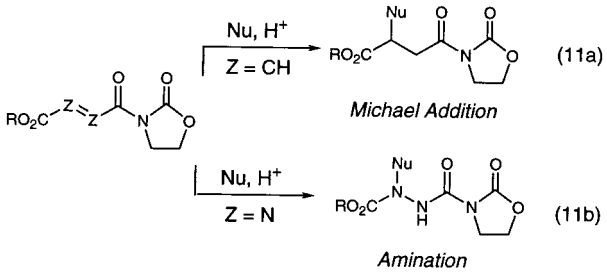


FIGURE 5. Stereochemical model for enantioselective Michael additions to alkylidene malonates.

approach might accentuate the differences in the diastereomeric transition states by bringing the nucleophile in closer proximity to the ligand chirality, an effect that was originally noted by Heathcock in diastereoselective additions to carbonyls.[32] For smaller β-substituents, the angle θ should be smaller and the effect lessened (e.g., R = Et, 22% ee), but the intervention of diastereomeric complexes cannot be discounted.

Enol Amination. Lewis acid-promoted amination of enols could provide a catalytic route to α-amino acids, an alternative to the amination of chiral imide enolates previously developed by our group.[33] This project has provided an important extension of the chelating substrate paradigm (eq 11a), wherein an azo compound functions as a conjugate acceptor for enolsilane nucleophiles (eq 11b).[34]

The [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a** was optimal for promoting the enantioselective conjugate addition of enolsilanes to the azaimide **9**. (*Z*) Enolsilanes of aryl ketones and related substrates react with **9** with greater than 96% enantioselection (Figure 6, eqs 12−15). The use of a protic additive was again critical to achieving catalyst

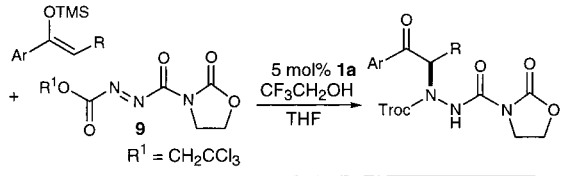


turnover to decompose the presumed hetero Diels−Alder intermediate observed by IR spectroscopy. The amination reaction is notable for the broad range of substitution tolerated on the nucleophilic component and for its complete regioselectivity. While both nitrogen centers are electronically activated for nucleophilic attack, the dominance of the imide-activated pathway highlights the importance of substrate chelation in these additions.

Aldol Additions. While the applications outlined above have relied on a six-membered chelate ring to provide organization in the catalyst−substrate complex, five-membered chelates may also function effectively in this capacity. We selected the aldol addition, a reaction in which our laboratory has had a long-standing interest, as a means to evaluate this hypothesis.

The discovery that enolsilane additions to (α-benzyloxy)acetaldehyde were highly enantioselective when catalyzed by the [Cu-Ph-pybox](SbF$_6$)$_2$ complex triggered our activity in this area (eq 16, Figure 7).[35] While the substrate generality for the nucleophilic component in this process was broad, we were frustrated in our efforts to find other electrophiles that would participate in enantioselective aldol reactions. The surprising lack of selectivity for (α-benzylthio)acetaldehyde, ethyl glyoxylate, and (β-benzyloxy)acetaldehyde, substrates that should engage in chelates structurally similar to that of (α-benzyloxy)acetaldehyde, was not easily rationalized.

We suspected that α-keto esters might engage in bidentate coordination to a chiral Cu(II) Lewis acid. Indeed, the [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a** was an



Ar	R	T (°C)	% yield[c]	% ee[d]	time[e]
Ph	Me	-20	95	99	2 min
4'-MeOPh	Me	-20	96	99	<1 min
6'-MeONap[a]	Me	-20	96	99	1 min
Ph	Et	-20	93	98	0.5 h
Ph	Allyl	-20	92	97	2 h
Ph	^{i}Bu	-20	92	98	2 h
Ph	^{i}Pr	-20	86	99	3h
4'-MeOPh	^{t}Bu	-20	84[f]	98	(6 h)
4'-MeOPh	Bn	-20	88	91	3 min
4'-MeOPh	Bn	-78	94	99	(12 h)
4'-MeOPh	Ph	-20	95	91	(2 h)

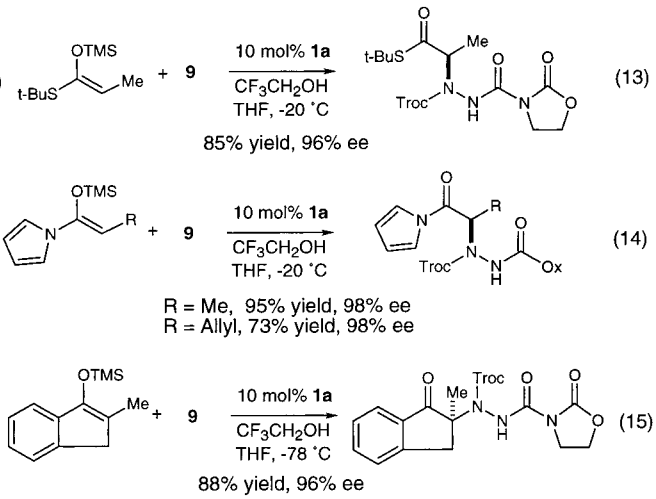


FIGURE 6. Representative enantioselective enolsilane aminations catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**1a**).

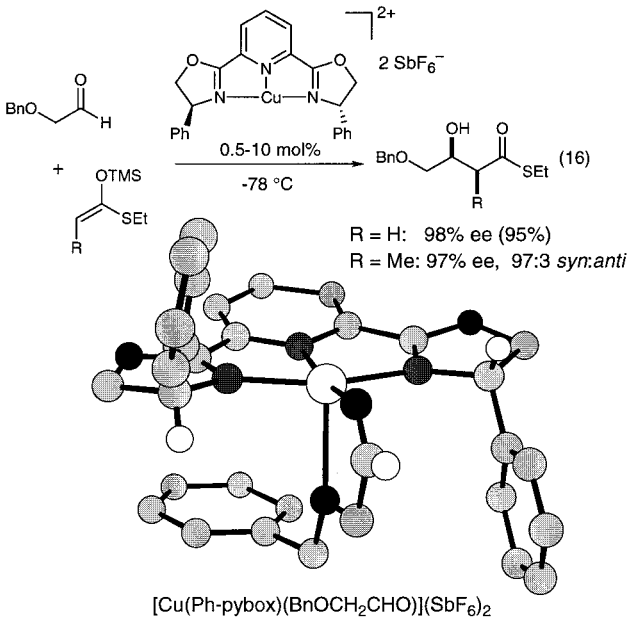
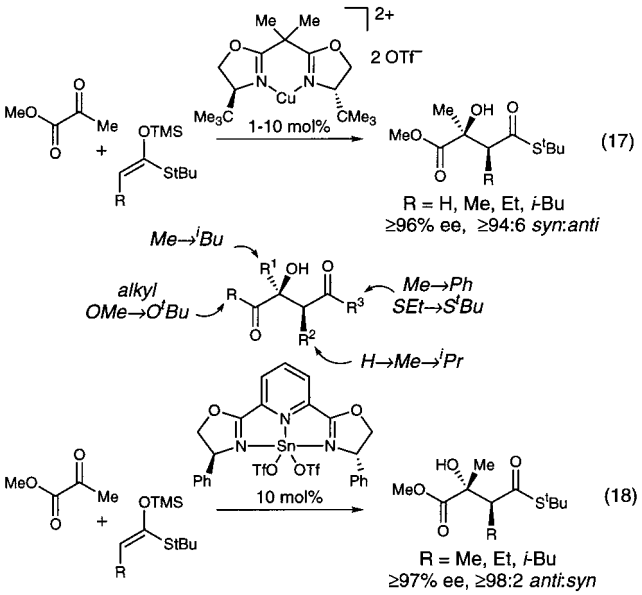


FIGURE 7. X-ray structure of catalyst substrate complex (counterions not shown).

effective catalyst for the addition of enolsilanes to pyruvate esters.[36] An examination of the reaction components revealed the generality of the process: highly diastereo- and enantioselective additions were feasible with a broad range of α-keto ester and α-diketone electrophiles and enolsilane nucleophiles (eq 17). Complementary to the *syn* diastereoselectivity observed with **1a**, the [Sn((*S*,*S*)-Ph-pybox)](OTf)$_2$ complex preferentially delivers *anti* aldol adducts in high enantioselectivity (eq 18).[3] Interestingly,



addition of an exogenous Me_3Si^+ source (TMSOTf) accelerated turnover in the Cu(II)-catalyzed reactions *without catalyzing a competing racemic aldol pathway*, again highlighting the importance of substrate chelation in the activation of bidentate electrophiles. To our knowledge, this work represents the first catalytic enantioselective addition of enolsilanes to pyruvate esters. The method

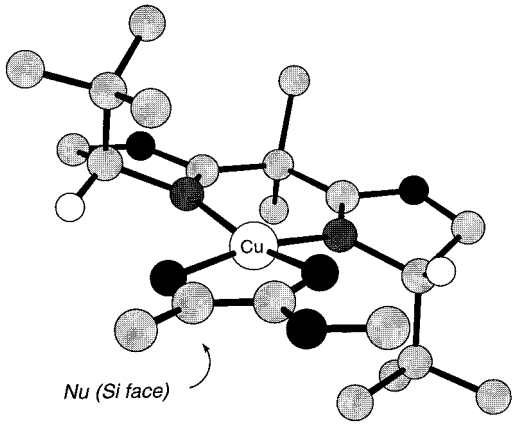


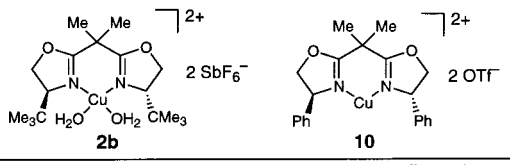
FIGURE 8. PM3-calculated structure of [Cu(*S*,*S*)-*t*-Bu-box)(pyruvate)]$^{2+}$.

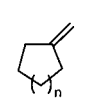
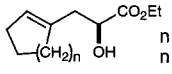
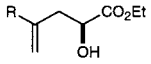
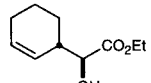
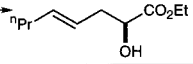
allows access to chiral tertiary alcohols and substituted succinic acid derivatives, important constituents in numerous natural products and pharmaceutical agents.

In the absence of an X-ray structure of the catalyst−substrate complex, a number of exercises were undertaken to rationalize the stereochemical outcome of the aldol reaction. A PM3 semiempirical calculation of the [Cu((*S*,*S*)-*t*-Bu-box)(pyruvate)]$^{2+}$ complex revealed a distorted square planar geometry, in analogy to the [Cu((*S*,*S*)-*t*-Bu-box)-(acrylimide)]$^{2+}$ structure (Figure 8). The absolute configuration of the adducts was again consistent with nucleophilic approach to the prochiral face opposite the *tert*-butyl substituent. The existence of a square planar complex in solution was verified by EPR spectroscopy of the binary [Cu((*S*,*S*)-*t*-Bu-box)(pyruvate)](OTf)$_2$ complex. Additionally, the observed enantioselectivities between −78 and 25 °C were consistent with those predicted by Arrhenius theory, supporting the hypothesis that enantioselection for this process was only a reflection of energy differences between two diastereomeric transition states, effectively excluding the intervention of alternate metal geometries. When this is considered in conjunction with the double stereodifferentiating experiments performed in the Diels−Alder studies, a unified picture of catalyst architecture begins to emerge. Uniform binding modes are enforced for substrates undergoing activation by the [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes as a result of a reluctance to adopt alternate metal geometries. This torsional rigidity restricts access to other potentially reactive conformations that could compromise enantiofacial discrimination. In contrast, Eyring plots for aldol reactions catalyzed by Cu(pybox) complexes do not exhibit a linear correlation between $1/T$ and ln(% major/% minor), a result that could be attributed to the low interconversion barrier between square pyramidal and trigonal pyramidal complexes or the intervention of other nonselective pathways.

Carbonyl Ene Reactions.[37] The dicarbonyl moiety was an effective structural motif for another addition reaction catalyzed by the [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complex. Ethyl glyoxylate was found to react with the full range of unactivated olefins to afford γ,δ-unsaturated α-hydroxy esters in high enantioselectivity (Table 3).[38] Several at-

Table 3. Catalyzed Glyoxylate Ene Reactions



alkene	product	%ee, config. (cat. **1b** or **2b**)	%ee, config. (cat. **10**)
		n = 1 96, *S* (**2b**) n = 2 97, *S* (**2b**)	76, *R* 87, *R*
		R = Me 96, *S* (**2b**) R = Ph 93, *S* (**2b**) R = $CH_2{}^nBu$ 89, *S* (**2b**)[a] R = $CH_2OTBDPS$ 96, *S* (**2b**)[c] R = CH_2OBn 98, *S* (**2b**)[c]	92, *R* 89, *R* 91, *R*[b] 91, *R*[c] 92, *R*[c]
		98, *S* (**1b**)[d]	94, *R*[e]
		98, *S* (**1b**)[f]	–

[a] Regioselection 74:26. [b] Regioselection 90:10. [c] Only isolated regioisomer. [d] *endo:exo* 86:14. [e] *endo:exo* 95:5. [f] (*E*):(*Z*) 96:4.

tractive features were noted in these reactions. [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ complex **2b** was typically as effective as the analogous anhydrous [Cu((*S*,*S*)-*t*-Bu-box)]-$(SbF_6)_2$ complex **1b**, in analogy with the Diels–Alder chemistry described previously. The aqua complex **2b**, a bench-stable pale blue powder that can be stored indefinitely without special precaution, provided not only uniformly high levels of enantioselection but also excellent control of regio- and diastereoselectivity. Notably, weakly nucleophilic olefins such as 1-hexene and cyclohexene had not been previously employed in catalytic asymmetric ene reactions, a testament to the Lewis acidity of the Cu(II) complexes.

The observed enantioselectivity for the glyoxylate ene reaction catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)]$(SbF_6)_2$ complexes was consistent with the chelation models previously proposed for imide and pyruvate ester substrates. The [Cu((*S*,*S*)-Ph-box)]$(OTf)_2$ complex **10** was also an effective catalyst *but provided the opposite product enantiomer*, an observation that was made contemporaneously in our hetero Diels–Alder studies (vide infra). This enantioselectivity turnover, originally noted by Jørgensen and Johannsen, is clearly inconsistent with the steric model developed for the *tert*-butyl-box catalyst.[37] Jørgensen has ascribed the selectivity reversal to a change in metal center geometry from square planar (*tert*-butyl) to tetrahedral (phenyl) (Figure 9). We have failed to uncover any conclusive evidence for or against this proposal, but we do note that, in the solid state, the phenyl complex **6** exhibits a *reduced* propensity to deviate from square planarity compared with **2b**.[20b]

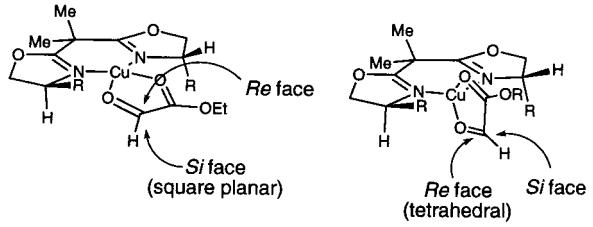
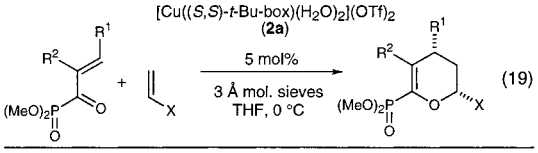


FIGURE 9. Square planar and tetrahedral Cu(II) stereochemical models.

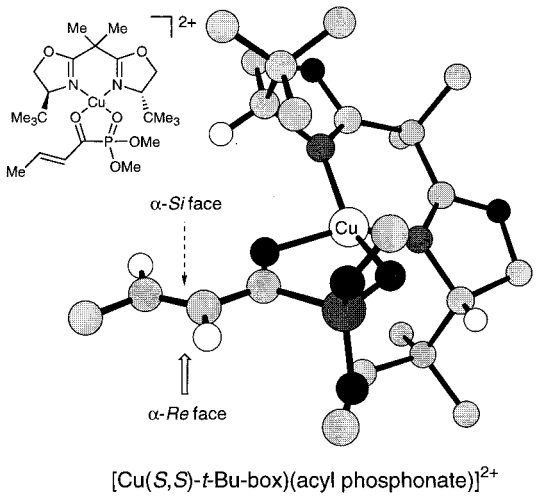
Hetero Diels–Alder Reactions. Chiral bis(oxazoline) Cu(II) complexes enantioselectively catalyze inverse electron demand hetero Diels–Alder reactions of acyl phosphonates[39] and enol ethers (eq 19), suggesting that the vicinal C=O and P=O functionalities can also fulfill our chelation criterion. The facial bias for the *tert*-butyl catalyst was correctly predicted by the chelation model (Figure 10).[40] A simple reaction protocol employing aquo complex **2a** at 0 °C renders this method attractive from a practical standpoint. We took care to ensure that the hetero Diels–Alder reaction (and all others described in this Account) could be conducted on multigram scale without loss of yield or selectivity. Consistent with our observations in the ene reaction, the [Cu((*S*,*S*)-Ph-box)]$(X)_2$ complexes afforded products enantiomeric to those obtained with the [Cu((*S*,*S*)-*t*-Bu-box)]$(X)_2$ complexes, frequently with enhanced levels of selectivity. Facile extension of this hetero Diels–Alder chemistry to α-keto ester heterodienes was achieved by us[41] and by Jørgensen et al.[42] (eq 20). High levels of enantioselection were obtained with γ-alkyl-, -aryl-, -alkoxy-, and -thioalkyl-substituted β,γ-unsaturated α-keto esters using 2 mol % of aquo complex **2a** (0 °C; typical reaction time 15–30 min). The use of hexane, a solvent in which complex **2a** is apparently insoluble, allowed us to reuse the solid catalyst multiple times through a simple recycling protocol.

We have not studied normal electron demand hetero Diels–Alder reactions, but reports from other groups have documented the feasibility of employing bis(oxazoline) Cu(II) complexes as catalysts for cycloadditions of this type. Notably, Jnoff and Ghosez have demonstrated that azadienes participate in enantioselective Diels–Alder reactions with imide dienophiles to yield substituted piperidones (eq 21),[43] while Jørgensen et al. have found that glyoxylate and pyruvate esters are good heterodienophiles in enantioselective hetero Diels–Alder reactions with siloxydienes (eq 22).[37,44] The azadiene reactions are stereospecific, with retention of diene geometry, but no information is available for the glyoxylate/pyruvate substrates since the configuration of the primary cycloadduct (prior to –OMe elimination) has not been reported. Ghosh observed mixtures of aldol and hetero Diels–Alder products in Cu(II)-catalyzed reactions of glyoxylate esters and siloxydienes, suggesting that the mechanism for these reactions could be stepwise, not concerted.[45]

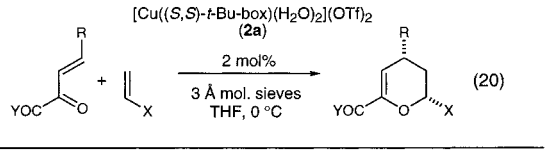
Conclusion. The constraints of the multistep synthesis experience provide the impetus for reaction development. Our laboratory relies on natural product total synthesis



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



[Cu(*S*,*S*)-*t*-Bu-box)(acyl phosphonate)]$^{2+}$



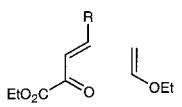
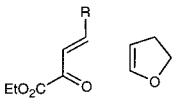
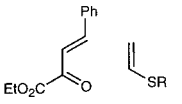
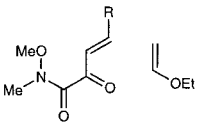
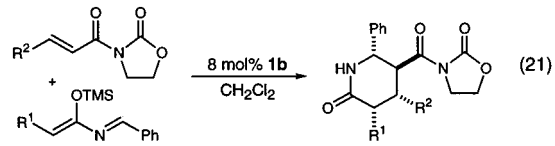
hetero diene	dienophile	product (*endo*/*exo*)	yield (%)	% ee
		R = Me (24:1)	87	97
		R = Ph (>20:1)	93	97
		R = ^{i}Pr (22:1)	95	96
		R = OMe (59:1)	90	98
		R = SBn (>20:1)	97	99
		R = Ph (16:1)	96	97
		R = ^{i}Pr (16:1)	94	95
		R = Et (>20:1)	94	97
		R = Ph (>20:1)	91	99
		R = Me (64:1)	99	99
		R = OMe (10:1)	94	98

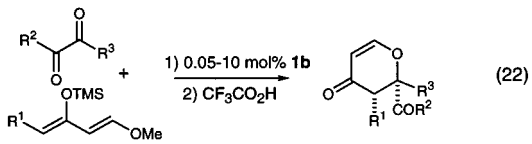
FIGURE 10. Representative hetero Diels–Alder Reactions catalyzed by [Cu((*S*,*S*)-*t*-Bu-box)(H_2O)$_2$](OTf)$_2$ (**2a**). PM3-calculated structure of [Cu(*S*,*S*)-*t*-Bu-box)(acyl phosphonate)]$^{2+}$.

to highlight shortcomings in existing methodology and attempts to bridge these gaps through the development of new catalytic processes. Because this is a long-term goal, we are less interested in simply finding selective reactions than we are in understanding the structural and mechanistic features that work in concert to provide that selectivity.

For the past decade, we have studied the chemistry of bis(oxazoline) copper complexes. Work to date has revealed that these and structurally related complexes provide a rigid square planar template with a defined chiral environment and catalyze a broad selection of reactions yielding valuable enantiomerically enriched compounds. Reactions of chelating substrates catalyzed by the [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes are stereoregular, the observed absolute configurations being consistent with a productive square planar catalyst–substrate binary complex. Those compounds that appear to successfully engage in chelation are acyl oxazolidinones, alkylidene malonates, glyoxylate and pyruvate esters, α-benzyloxyacetaldehyde, vicinal diketones, α-keto amides, and acyl phosphonates.[46] X-ray crystallography, in situ IR spectroscopy, EPR spectroscopy, semiempirical calculations, and double stereodifferentiating experiments have been valuable tools for studying these complexes and the reactions they catalyze. The practical benefits of the



R^1	R^2	T °C	*endo*/*exo*	yield (%)	% ee
Me	Me	-45	>99:1	80	95
Me	Me	rt	>99:1	96	94
H	H	-45	6:1	83	98
Me	H	-45	>99:1	96	98
H	Me	rt	>99:1	80	93



R^1	R^2	R^3	T °C	yield (%)	% ee
Me	OEt	H	-78	96	99
Me	Et	H	-40	77	98
Me	Ph	H	-40	75	96
Ph	OEt	Me	-40	57	99
Me	Me	Me	-40	60	91

reactions described herein include facile preparative-scale applications and relative insensitivity to reaction temperature (Figure 11). Taken as a whole, the work from our laboratory and the contributions of others suggests that

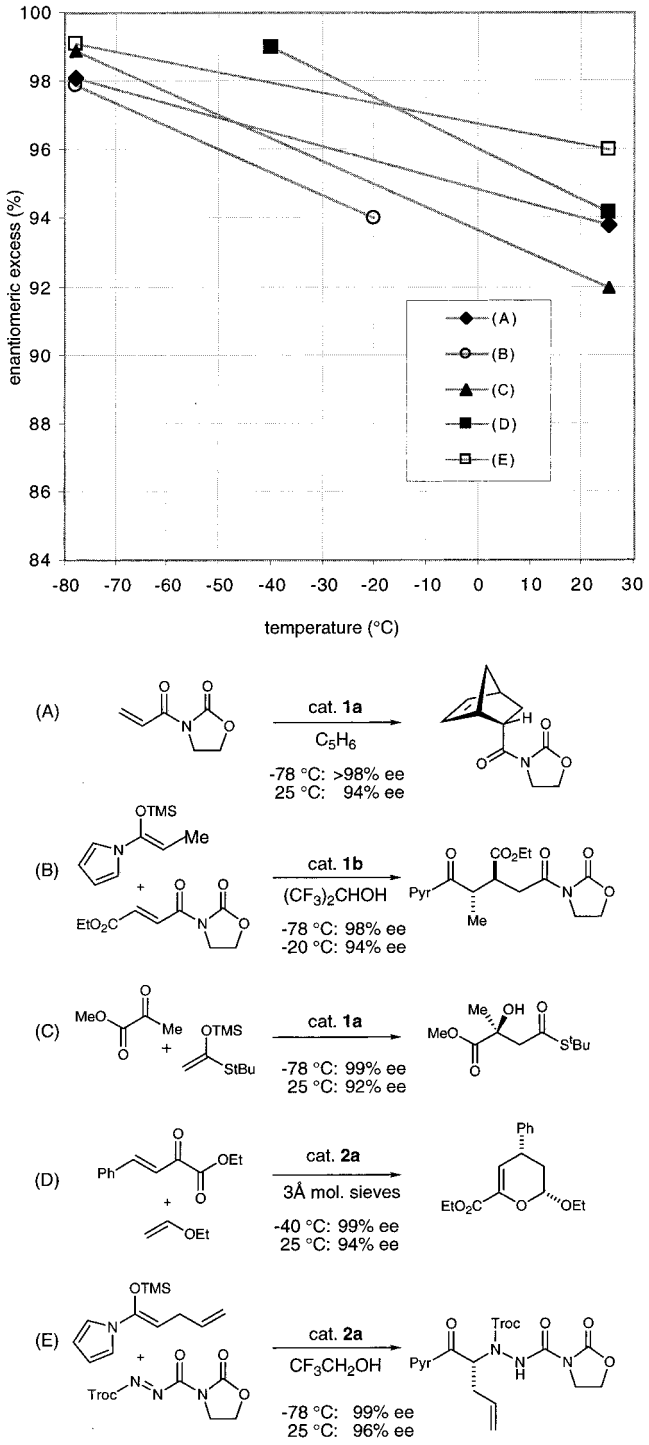


FIGURE 11. Temperature−enantioselectivity profiles for representative Cu(II)-catalyzed reactions.

we are approaching the goal of employing bis(oxazoline) copper(II) complexes as generally useful enantioselective catalysts.

We thank our co-workers, David Barnes, Chris Burgey, Kevin Campos, Brian Connell, Jake Janey, Doug Johnson, Jeff Johnston, Marisa Kozlowski, Tom Lectka, David MacMillan, Peter von Matt, Scott Miller, Jerry Murry, Roger Norcross, Ed Olhava, Nick Paras, Gretchen Peterson, Tom Rovis, Eileen Shaughnessy, Richard Staples, Jason Tedrow, Steven Tregay, Tomas Vojkovsky, Michael Willis, and Keith Woerpel, who are responsible for the experimental and intellectual advances described in this Account. Their specific contributions are acknowledged in the references. Funding for this research was provided by the National Science Foundation and National Institutes of Health. The amino alcohols and amino acids used in the preparation of the box ligands were generously provided by NSC Technologies. J.S.J. acknowledges graduate fellowships from the NSF, Pharmacia and Upjohn, and Roche.

References

(1) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: New York, 1996.
(2) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. Cationic Bis(oxazoline) and Pyridyl-bis(oxazoline)Cu(II) and Zn(II) Lewis Acid Catalysts. A Comparative Study in Catalysis of Diels−Alder and Aldol Reactions. *Tetrahedron Lett.* **1996**, *37*, 7481−7484.
(3) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. C_2-Symmetric Tin(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Anti Aldol Additions of Enolsilanes to Glyoxylate and Pyruvate Esters. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.
(4) (a) Pfaltz, A. Chiral Semicorrins and Related Nitrogen Heterocycles as Ligands in Asymmetric Catalysis. *Acc. Chem. Res.* **1993**, *26*, 339−345. (b) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. C_2-Symmetric chiral bis(oxazoline)-metal complexes in catalytic asymmetric synthesis. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (c) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. Catalytic Asymmetric Addition Reactions of Carbonyls. A Common Catalytic Approach. *Acc. Chem. Res.* **1999**, *32*, 605−613.
(5) Evans, D. A.; Chapman, K. T.; Bisaha, J. Asymmetric Diels−Alder Cycloaddition Reactions With Chiral α,β-Unsaturated N-Acyloxazolidinones. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256 and references therein.
(6) Castellino, S.; Dwight, W. J. Et_2AlCl Complexes of an N-Acyloxazolidinone−NMR Investigation. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987.
(7) Irving, H.; Williams, J. P. The Stability of Transition-metal Complexes. *J. Chem. Soc.* **1953**, 3192−3210.
(8) Hathaway, B. J. Copper. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1987; Vol. 5, Chapter 53.
(9) Hathaway, B. J.; Billing, D. E. The Electronic Properties and Stereochemistry of Mono-nuclear Complexes of the Copper(II) Ion. *Coord. Chem. Rev.* **1970**, *5*, 143−207.
(10) (a) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. Lewis acid Catalysis of a Diels−Alder Reaction in Water. *J. Am. Chem. Soc.* **1996**, *118*, 7702−7707. See also: (b) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. A Chiral Lewis-Acid-Catalyzed Diels−Alder Reaction. Water-Enhanced Enantioselectivity. *J. Am. Chem. Soc.* **1998**, *120*, 4238−4239.
(11) For a more thorough review of this topic, see: Dias, L. C. Chiral Lewis acid catalysts in Diels−Alder cycloadditions: Mechanistic aspects and synthetic applications of recent systems. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332.
(12) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. Asymmetric Diels−Alder Reaction Catalyzed By a Chiral Titanium Reagent. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345.
(13) Corey, E. J.; Imai, N.; Zhang, H. Y. Designed Catalyst For Enantioselective Diels−Alder Addition From a C_2-Symmetrical Chiral Bis(oxazoline)-Fe(III) Complex. *J. Am. Chem. Soc.* **1991**, *113*, 728−729.
(14) Corey, E. J.; Ishihara, K. Highly Enantioselective Catalytic Diels−Alder Addition Promoted By a Chiral Bis(oxazoline)-Magnesium Complex. *Tetrahedron Lett.* **1992**, *33*, 6807−6810.
(15) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. Bis(oxazolines) As Chiral Ligands in Metal-Catalyzed Asymmetric Reactions: Catalytic, Asymmetric Cyclopropanation of Olefins. *J. Am. Chem. Soc.* **1991**, *113*, 726−728.
(16) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. Bis(oxazoline) Copper-Complexes As Chiral Catalysts For the Enantioselective Aziridination of Olefins. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329.
(17) Evans, D. A.; Miller, S. J.; Lectka, T. Bis(oxazoline)Copper(II) Complexes As Chiral Catalysts For the Enantioselective Diels−Alder Reaction. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461.
(18) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. Chiral Bis(oxazoline)copper(II) Complexes as Lewis Acid Catalysts for the Enantioselective Diels−Alder Reaction. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.

(19) Subsequent to this study, other chiral metal complexes have been reported as catalysts for these Diels–Alder reactions. For a review of these advances, see ref 18.
(20) (a) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. An Improved Procedure for the Preparation of 2,2-bis[2-[4(*S*)-*tert*-butyl-1,3-oxazolinyl]]propane [(*S,S*)-*tert*- butylbis(oxazoline)] and Derived Copper(II) Complexes. *J. Org. Chem.* **1998**, *63*, 4541–4544. (b) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. Reversal in Enantioselectivity of *tert*-Butyl Versus Phenyl-Substituted Bis(oxazoline) Copper(II) Catalyzed Hetero Diels–Alder and Ene Reactions. Crystallographic and Mechanistic Studies. *Tetrahedron Lett.* **1999**, *40*, 2879–2882.
(21) Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W. A.; Blake, G. A. Benzene Forms Hydrogen-Bonds With Water. *Science* **1992**, *257*, 942–944.
(22) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. C_2-Symmetric Cationic Copper(II) Complexes As Chiral Lewis Acids: Counterion Effects in the Enantioselective Diels–Alder Reaction. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800.
(23) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. Bis(oxazoline) and Bis(oxazolinyl)pyridine Copper Complexes as Enantioselective Diels–Alder Catalysts. Reaction Scope and Synthetic Applications. *J. Am. Chem. Soc.* **1999**, *121*, 7582–7594.
(24) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. Cationic Bis-(oxazoline)Cu(II) Lewis Acid Catalysts. Application to the Asymmetric Synthesis of *ent*-Δ^1-tetrahydrocannabinol. *Tetrahedron Lett.* **1997**, *38*, 3193–3194.
(25) Evans, D. A.; Johnson, J. S. Chiral C_2-Symmetric Cu(II) complexes as Catalysts for Enantioselective Intramolecular Diels–Alder Reactions. Asymmetric Synthesis of (–)-Isopulo'upone. *J. Org. Chem.* **1997**, *62*, 786–787.
(26) Evans, D. A.; Barnes, D. M. Cationic Bis(oxazoline)Cu(II) Lewis acid catalysts. Enantioselective Furan Diels–Alder Reaction in the Synthesis of *ent*-Shikimic Acid. *Tetrahedron Lett.* **1997**, *38*, 57–58.
(27) (a) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. The Influence of Ligand Bite Angle on the Enantioselectivity of Copper(II)-catalysed Diels–Alder Reactions. *Chem. Commun.* **1996**, 1753–1754. (b) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. Application of Indane-derived C_2-Symmetric Bis-(oxazolines) in Two-point Binding Asymmetric Diels–Alder Reactions. *Tetrahedron Lett.* **1996**, *37*, 1725–1726.
(28) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. Conformationally constrained bis(oxazoline) derived chiral catalyst: a highly effective enantioselective Diels–Alder reaction. *Tetrahedron Lett.* **1996**, *37*, 3815–3818. (b) Ghosh, A. K.; Cho, H.; Cappiello, J. Bis-(oxazoline) derived cationic aqua complexes: highly effective catalysts for enantioselective Diels–Alder reactions. *Tetrahedron Asymmetry* **1998**, *9*, 3687–3691.
(29) Evans, D. A.; Willis, M. C.; Johnston, J. N. C_2-Symmetric Copper-(II) Complexes as Chiral Lewis Acids. Catalytic Stereoselective Michael Additions to Unsaturated Ester Derivatives. *Org. Lett.* **1999**, *1*, 865–868.
(30) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Michael Addition of Silylketene Acetals to Alkylidene Malonates. *J. Am. Chem. Soc.* **1999**, *121*, 1994–1995.
(31) Krapcho, A. P. Synthetic Applications of Dealkoxycarbonylations of Malonate Esters, β-Keto Esters, α-Cyano Esters and Related Compounds in Dipolar Aprotic Media—Part 1. *Synthesis* **1982**, 805–822.
(32) Heathcock, C. H. Understanding and Controlling Diastereofacial Selectivity in Carbon–Carbon Bond-forming Reactions. *Aldrichimica Acta* **1990**, *23*, 99–111 and references therein.
(33) (a) Evans, D. A.; Britton, T. C.; Dellaria, J. F. The Asymmetric Synthesis of α-Amino and α-Hydrazino Acid Derivatives via the Stereoselective Amination of Chiral Enolates with Azodicarboxylate Esters. *Tetrahedron* **1988**, *44*, 5525–5540. For a catalyst-controlled approach, see: (b) Evans, D. A.; Nelson, S. G. Chiral Magnesium Bis(sulfonamide) Complexes as Catalysts for the Merged Enolization and Enantioselective Amination of *N*-Acyloxazolidinones. A Catalytic Approach to the Synthesis of Arylglycines. *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453.
(34) Evans, D. A.; Johnson, D. S. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Amination of Enolsilanes. *Org. Lett.* **1999**, *1*, 595–598.
(35) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Silylketene Acetals to (Benzyloxy)-acetaldehyde. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of Catalytic Enantioselective Aldol Additions of Enolsilanes to (Benzyloxy)-acetaldehyde. *J. Am. Chem. Soc.* **1999**, *121*, 669–685.
(36) (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Esters. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of the Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Esters. *J. Am. Chem. Soc.* **1999**, *121*, 686–699.
(37) Jørgensen has reported mixtures of ene and hetero Diels–Alder adducts in catalyzed reactions of glyoxylate esters and dienes: (a) Johannsen, M.; Jørgensen, K. A. Asymmetric Hetero-Diels–Alder Reactions and Ene Reactions Catalyzed By Chiral Copper-(II) Complexes. *J. Org. Chem.* **1995**, *60*, 5757–5762. (b) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. Metal-catalyzed Asymmetric Hetero-Diels–Alder Reactions of Unactivated Dienes with Glyoxylates. *Pure Appl. Chem.* **1998**, *70*, 1117–1122.
(38) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Enantioselective Catalysis of the Glyoxylate-Ene Reaction. *J. Am. Chem. Soc.* **1998**, *120*, 5824–5825.
(39) (a) Schuster, T.; Evans, S. A. Hetero-Diels–Alder Reactions of Dimethyl 1-Oxo-(E,E)-2,4-Hexadienephosphonate with 2-Alkylidene-1,3-Dithianes. *Phosphorus Sulfur Silicon Relat. Elem.* **1995**, *103*, 259–271. (b) Telan, L. A.; Poon, C. D.; Evans, S. A. Diastereoselectivity in the Mukaiyama-Michael Reaction Employing α-Acyl β,γ-Unsaturated Phosphonates. *J. Org. Chem.* **1996**, *61*, 7455–7462.
(40) (a) Evans, D. A.; Johnson, J. S. Catalytic Enantioselective Hetero Diels–Alder Reactions of α,β-Unsaturated Acyl Phosphonates with Enol Ethers. *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. Enantioselective Synthesis of Dihydropyrans: Catalysis of Hetero Diels–Alder Reactions by Bis(oxazoline) Copper(II) Complexes. In press.
(41) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. Chiral C_2-Symmetric Cu(II) Complexes as Cata-lysts for Enantioselective Hetero Diels–Alder Reactions. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375.
(42) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. Highly Enantioselective Catalytic Hetero-Diels–Alder Reaction with Inverse Electron Demand. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404–2406.
(43) Jnoff, E.; Ghosez, L. Asymmetric Diels–Alder Reactions of 2-Azadienes Catalyzed by a Chiral Copper(II) Complex. A General Route to Enantiomerically Pure Piperidones. *J. Am. Chem. Soc.* **1999**, *121*, 2617–2618.
(44) Yao, S. L.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. Catalytic Asymmetric Hetero-Diels–Alder Reactions of Ketones: Chemzymatic Reactions. *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605 and references therein.
(45) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. Asymmetric Hetero Diels–Alder Reactions of Danishefsky's Diene and Glyoxylate Esters Catalyzed by Chiral Bisoxazoline Derived Catalysts. *Tetrahedron: Asymmetry* **1996**, *7*, 2165–2168.
(46) Chelation is being exploited as a key feature in the development of enantioselective radical reactions: Sibi, M. P.; Porter, N. A. Enantioselective Free Radical Reactions. *Acc. Chem. Res.* **1999**, *32*, 163–171.

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