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Chiral copper(II) complexes as Lewis acids for catalyzed cycloaddition, carbonyl addition, and conjugate addition reactions*

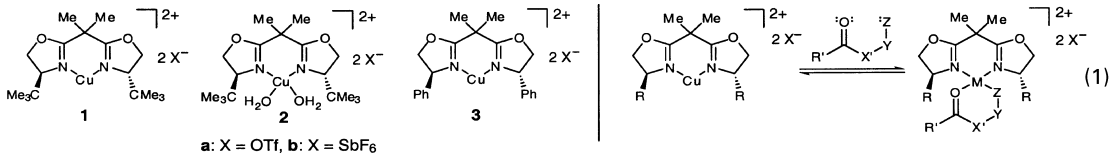
David A. Evans,† Tomislav Rovis and Jeffrey S. Johnson

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

Abstract: Bis(oxazoline) copper(II) complexes **1–3** function as enantioselective Lewis acid catalysts for carbocyclic and hetero Diels–Alder, aldol, Michael, ene, and amination reactions with substrates capable of chelation. X-ray crystallography of the catalyst reveals a propensity for the formation of distorted square planar or square pyramidal complexes. 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** resulting from the intervention of a distorted square planar catalyst-substrate binary complex.

INTRODUCTION

Many organic reactions are subject to catalysis by metal complexes, and the use of chiral nonracemic complexes facilitates the efficient asymmetric synthesis of organic compounds. Notable examples include catalyzed group transfer reactions, oxidations, insertions, reductions of olefins and ketones, and carbonyl addition reactions. Considerable effort has also been expended in the discovery of chiral metal complexes that serve as Lewis acids [1]. Diels–Alder, aldol and Michael reactions, transformations that occupy a central position in organic chemistry, typically respond strongly to Lewis acid activation of one of the reacting partners as a result of perturbations in the relevant frontier molecular orbitals. A long-standing objective in our laboratory has been the development of chiral Lewis acidic complexes that might be suitable for the catalysis of a broad selection of carbon-carbon bond forming reactions. The successful application of C_2-symmetric bis(oxazoline) Cu(II) complexes **1–3**, as chiral chelating Lewis acids, Scheme 1, to enantioselective carbocyclic and hetero Diels–Alder, aldol, Michael, ene and amination reactions has resulted from our ongoing investigations. This manuscript is intended to provide an overview of our progress in this area and to provide insight into the factors that commonly affect diastereo- and enantioselection in these processes.



Scheme 1

In our own studies, Cu(II) emerged as a promising organizational center with regard to both reactivity and selectivity in approximately 1990 for the following reasons: Irving and Williams noted in 1953 that Cu(II) (d^9) forms the most stable complexes of the divalent metal ions in the first transition series (Mn < Fe < Co < Ni < **Cu** > Zn) [2]; conversely, the exchange rate of $[Cu(H_2O)_6]^{2+}$ is greater than other

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†*Corresponding author*: E-mail: evans@chemistry.harvard.edu

first row divalent transition metal ions, an effect consistent with labilization of axial ligands through Jahn–Teller distortion [3] and the presence of the odd electron which is accommodated in the ligand plane ($d_{(x2-y2)}$). The consequence of this apparent paradox is that the use of the chelating bis(oxazoline) ligand affords a thermodynamically stable complex which is kinetically labile with respect to more weakly bound ligands (e.g. carbonyl compounds). With regard to the binding and activation of substrates, recent work by Engberts and co-workers documents the advantages of Cu(II) relative to other metal ions in the first transition series [4]. Cu(2+) complexes also possess predictable coordination geometries. A strong bias is found for square planarity in 4-coordinate complexes with a high barrier to tetrahedral distortion. On the other hand, 5-coordinate Cu(2+) complexes are found in either trigonal bipyramidal or square pyramidal geometries, with a relatively low barrier to their interconversion.

High enantioselectivity is typically realized using the bis(oxazoline) Cu(II) system only when the substrate undergoing activation is capable of bidentate coordination to the chiral Lewis acid (Eqn 1). This criterion of chelation is apparently necessary to provide good catalyst-substrate organization before and/or during the bond-forming event.

CATALYST DEVELOPMENT

Structural characterization

In conjunction with our efforts to understand the coordination chemistry of Cu(II), a number of our bis(oxazoline) copper(II) complexes have been characterized using X-ray crystallography (Fig. 1). From the illustrated structures, the gross topography of these complexes remains constant; however, variations in counterion and ligand substitution strongly influence the architecture and coordination number. The structure of the hydrated [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(OTf)_2$ complex **2a** exhibits a distorted square pyramidal geometry with a weakly bound apical triflate ligand (Cu–OTf = 2.62 Å) [5]. The structure of the analogous SbF_6-derived [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ complex **2b** exhibits slightly larger distortions of the equatorial water ligands, but importantly, the counterions are fully dissociated (Cu–$FSbF_5$ = 3.30 Å) [6]. The distortions from square planarity are presumed to be largely induced by steric interactions, as the analogous [Cu((*S*,*S*)-*i*-Pr-box)$(H_2O)_2$]$(SbF_6)_2$ complex **4** exhibits smaller O-Cu-N-C dihedral angles [7]. The distortion of the water molecules actually reverses in the case of [Cu((*S*,*S*)-Ph-box)$(H_2O)_2$]$(SbF_6)_2$ complex **3b**: the ligands are oriented *toward* the oxazoline phenyl substituents. In contrast to complex **2b**, the counterions of both **4** and **3b** are associated with the metal center, probably as a result of increased steric accessibility (**4**: Cu–$FSbF_5$ = 2.52, 2.73 Å; **3b**: Cu–$FSbF_5$ = 2.44, 2.52 Å).

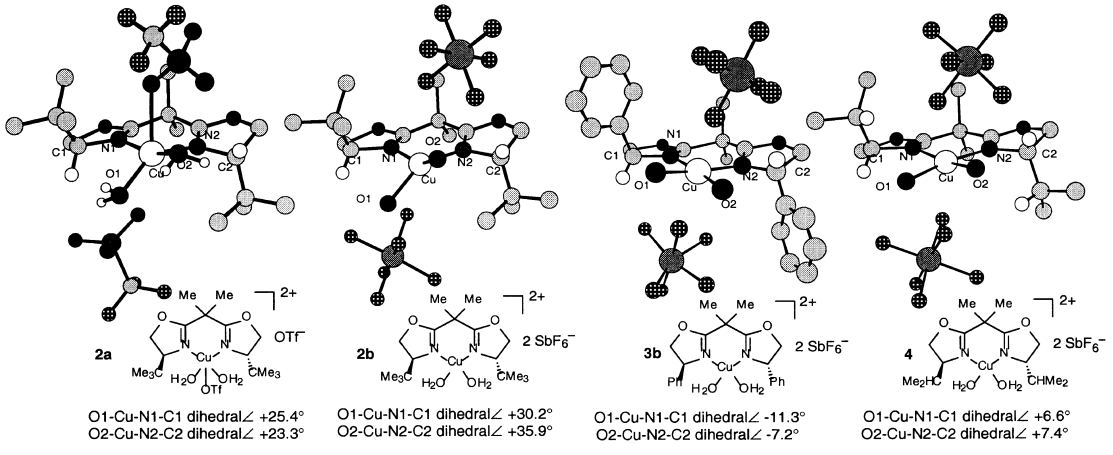
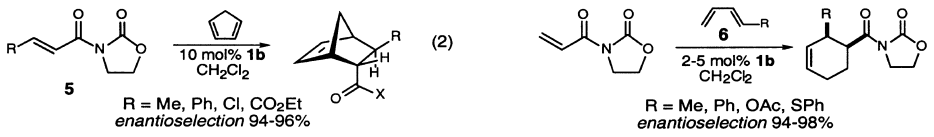


Fig. 1 X-ray crystal structures of Cu[bis(oxazoline)$(H_2O)_2$]$(X)_2$ complexes.

Diels–Alder reactions

Complexes **1a, 1b** and **2b** function as selective Diels–Alder catalysts with acryloyl imide dienophiles **5** (Scheme 2) [8]. The nature of the counterion is important: the more reactive hexafluoroantimonate-derived

complexes **1b** and **2b** were preferred in terms of both conferred enantioselectivity (94–98% enantiomer excess, 0–25 °C) and reaction rate [9]. Using cyclopentadiene, β-substituted imides (**5**, R ≠ H) afford the derived bicyclic adducts in uniformly excellent diastereo- and enantioselectivity (Eqn 2) [10]. With less reactive acyclic dienes **6**, the acrylimide **5** (R = H) selectively gives cyclohexene derivatives (Eqn 3) [11]. In many cases, the use of the isolable, bench-stable [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]$(SbF_6)_2$ complex **2b** (blue powder) affords results equivalent to those afforded by the anhydrous complex **1b**. Intramolecular applications are feasible [12], as are reactions using furan [13] and disubstituted dienes [14]. The synthetic utility of this system has been demonstrated [12–14].



Scheme 2

The absolute stereochemical outcome of these cycloadditions is regulated by the geometry of the metal complex and effective communication between the ligand chirality and prochiral olefin; semiempirical calculations of the catalyst substrate complex **7·PM3** suggest that the imide dienophile coordinates to the Lewis acid **1** with distortions similar to those observed in the solid state for hydrated complexes **2a** and **2b**. The bulky *tert*-butyl group provides a well-defined chiral environment and cycloaddition occurs from the α-*Re* face *with complete stereoregularity*. To assess whether the solid state geometry carries over into solution, double stereodifferentiating experiments were performed with chiral dienophiles known to participate in highly selective Diels–Alder reactions [15]. Unambiguous matched and mismatched catalyst-substrate complexes were obtained and provided support for the intervention of a square planar or square pyramidal species in solution (Fig. 2).

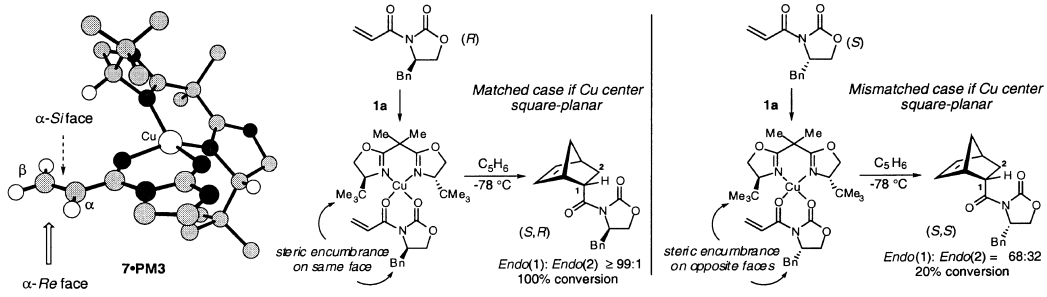


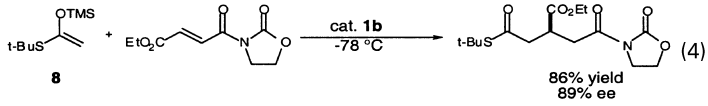
Fig. 2 Stereochemical models and double stereodifferentiating reactions of Diels–Alder reactions catalyzed by [Cu-(*S*,*S*)-*t*-Bu-box]X_2 complexes.

The preceding Diels–Alder study provided several pieces of information that were crucial for subsequent extensions. The first was the relative invariability of product enantioselectivity with reaction temperature, facilitating the use of experimentally convenient temperatures and broadened substrate scope. Second, the importance of counterion architecture was revealed. Finally, despite their strong Lewis acidity, Cu(II) catalysts tolerate donor and/or hydroxylic solvents.

Michael reactions of fumaroyl imides [16]

Building on the structural investigations conducted with respect to the Diels–Alder reaction, we reasoned that a similar level of π-facial discrimination should be observed in the conjugate addition of latent enolates, the Mukaiyama Michael reaction. Indeed, initial results bore testament to this fact, with silylketene acetal **8** adding to the fumarate derived imide in the presence of (Cu((*S*,*S*)-*t*-Bu-box))$(SbF_6)_2$ complex **1b** providing the Michael adduct in 86% yield and 89% enantiomer excess (Eqn 4; Scheme 3).

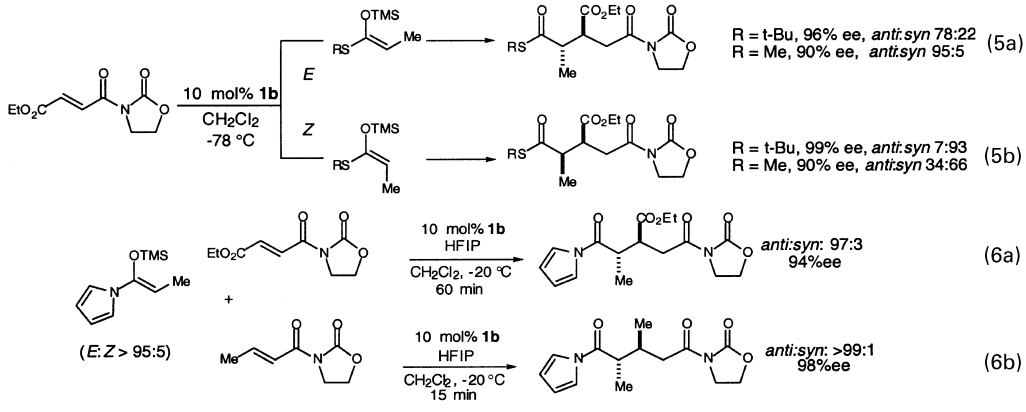
Diastereoselective Michael reactions proceed extremely well with slight tailoring of the reaction conditions (Eqn 5). Whereas the (*Z*) silylketene acetal derived from *S*-*t*-butyl thiopropionate is highly *syn*



Scheme 3

selective in the Michael addition with 93:7 selectivity and > 99% enantiomer excess of the major adduct, the corresponding (*E*) silylketene acetal is moderately selective to give the *anti* diastereomer with 78:22 selectivity in 96% enantiomer excess. Interestingly, the *S*-methyl thiopropionate is complementary: the (*Z*) silylketene acetal is moderately selective for the *syn* adduct (66:34, 90% enantiomer excess) but the (*E*) silylketene acetal is highly *anti* selective (95:5, 90% enantiomer excess). The synergism of these two parameters was found to be general in this series.

Early experiments in this area were plagued by long reaction times. A careful investigation by *in situ* IR spectroscopy revealed the presence of an intermediate accumulating during the course of the reaction. This intermediate ostensibly behaves as an inhibitor of the catalyst. As with several other reactions (*vide infra*), addition of an alcohol as an additive effectively served to promote catalyst turnover. Whereas typical reactions required > 72 h to proceed to completion in the absence of any additive, with one equivalent of $(CF_3)_2CHOH$ (HFIP) present, the reaction proceeded to completion in 4 h. Under these conditions, no intermediate could be observed by IR. Indeed, addition of HFIP to a stalled reaction caused an immediate decomposition of the intermediate with concomitant generation of product. We now have direct evidence that this intermediate is the dihydropyran 'cycloadduct' and that this reaction may be viewed as a hetero Diels–Alder reaction. The presence of the dihydropyran provides impetus for explaining the stereochemistry of this transformation. An ordered *endo* transition state, *via* a formal hetero Diels–Alder path, rationalizes the complementary effects of the isomeric silylketene acetals and the observed stereoselectivity. Ongoing studies in this area point to the broad utility of these addition reactions (Eqn 6; Scheme 4).

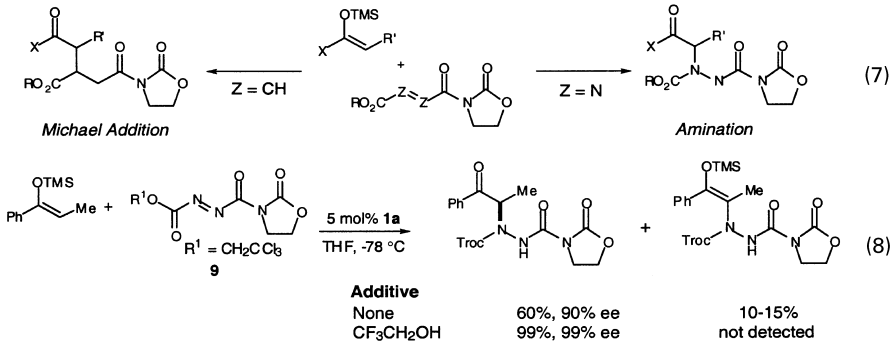


Scheme 4

Enol amination [17]

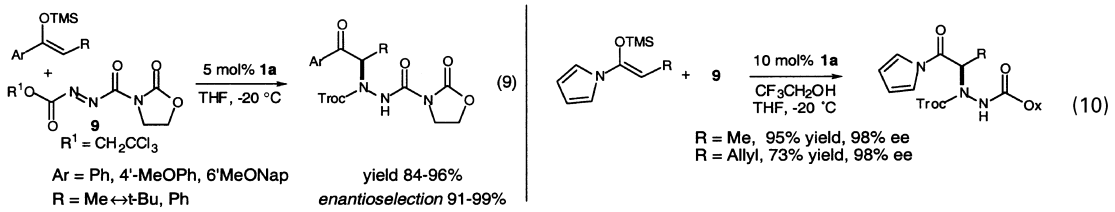
In direct analogy to the fumarate imide Michael reactions, we envisioned that a conjugate addition to an azo dicarboxylate equivalent would form α-amino carbonyls, a net amination of the enol moiety (Eqn 7) [18]. This work would provide a catalytic alternative to our previously developed stoichiometric reaction [19].

Initial investigations revealed that [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ complex **1a** was highly selective in catalyzing the amination of propiophenone enolsilane with azo-imide **9** (Eqn 8, Scheme 5). However, the reaction suffered from catalyst turnover. Typical catalytic reactions resulted in moderate yields of the desired product along with significant amounts of aminated enolsilane by-product. Presumably, the latter arose from internal proton transfer to the aza-enolate. Reasoning that an external proton source would alleviate this problem and allow for efficient catalyst turnover, one equivalent of trifluoroethanol (TFE)



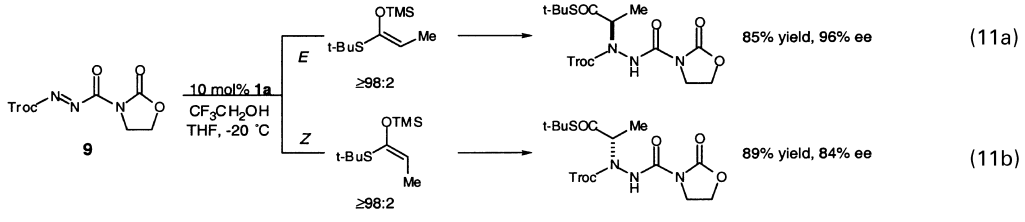
Scheme 5

was added. The reaction proceeded to completion in less than 1 h at –78 °C, in contrast to the extended reaction times in the absence of the alcohol (> 24 h). The reaction was found to be general with respect to substitution of the aryl ketones. Bulkier substituents required longer reaction times but proceeded in good yield and high selectivity when the more electron rich *p*-MeO phenyl ketones were used (Eqn 9; Scheme 6).



Scheme 6

Silylketene acetals derived from thioesters were subjected to the amination conditions with the aim of developing an approach to α-amino acids (Eqn 11). Not unexpectedly, this reaction proved to be very sensitive to enolsilane geometry: the two geometrical isomers lead to opposite enantiomers of the addition product. Although the enantioselectivity was high with (*E*) silylketene acetals, the use of the less reactive (*Z*) silylketene acetal resulted in lower selectivities. This problem was solved by the use of pyrrole derived silylketene acetals (Eqn 10). These are formed in selectivities > 99:1, yet the products are activated esters, providing an efficient, highly selective entry into α-amino acid derivatives (Scheme 6).



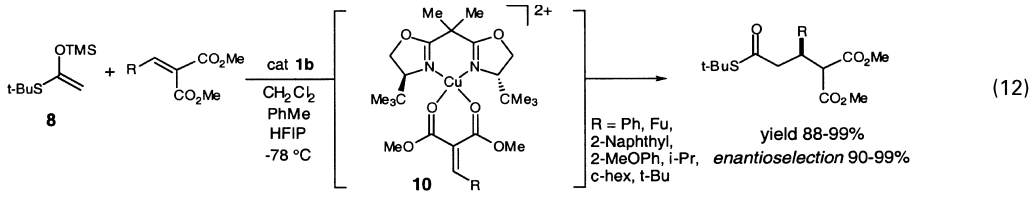
Scheme 7

Contrary to previously investigated systems, the prochiral moiety resides exclusively on the nucleophile. The electrophilic component serves to orient the incoming nucleophile with a net transmission of prochirality. Stereochemistry of the adducts is best rationalized invoking a formal hetero Diels–Alder intermediate. The noted preference for the OR substituent in an *endo* transition state also explains the facial turnover when changing enolsilane geometry. This mechanism is supported by the observation of an intermediate possessing an IR frequency of 1687 cm^{-1}, characteristic of a dihydrooxadiazene C=N stretch.

Michael reactions of alkylidene malonates [20]

Alkylidene malonates, readily available *via* Knoevenagel condensations, are also attractive Michael

acceptors. This substrate mandated a departure from the classic binding model. Whereas acryloyl imides place the olefin directly below the ligand in the reactive conformation, binding of the alkylidene malonates places the reacting center in the pseudo C_2 axis of the complex (cf. **10**, Eqn 12). It was not obvious that this catalyst-substrate geometry would lead to highly selective facial discrimination (Scheme 8).



(12)

Scheme 8

Initial results revealed that the hurdle in this reaction was again catalyst turnover rather than reaction selectivity. As expected, β-substituted alkylidene malonates were sufficiently reactive in the Mukaiyama Michael reaction, with the additions proceeding at –78 °C. However, no turnover was observed under these conditions. Suspecting that protonation/silyl transfer was again problematic, we conducted the reaction in the presence of hexafluoroisopropanol (HFIP) and observed successful turnover. Under these conditions, a variety of alkylidene malonates undergo highly selective Michael addition of silylketene acetal **8**, providing the adducts in enantiomer excesses of 90–99% and nearly quantitative yields (Eqn 12). The sole requirement for selective addition seems to be the presence of a β substituent of some steric bulk (when R is Et, the Michael adduct is formed in only 22% enantiomer excess).

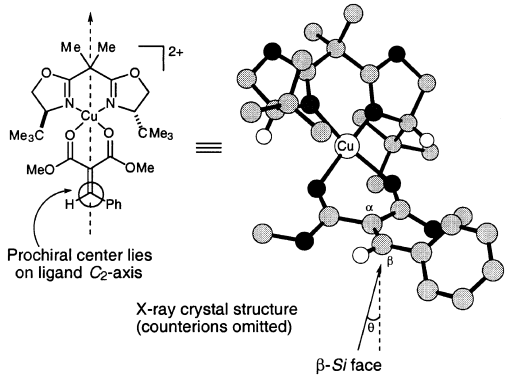


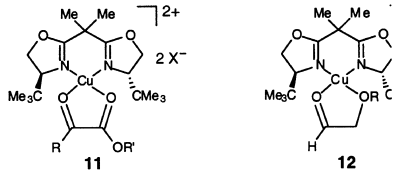
Fig. 3 Stereochemical model for enantioselective Michael additions to alkylidene malonates.

Characterization of the [Cu(*t*-Bu-Box)(alkylidene malonate)]$(SbF_6)_2$ complex was accomplished by X-ray crystallography. Significantly, this represents the first instance of crystallographic characterization of a substrate bound to a bis(oxazoline)Cu complex and validates our assumption (*vide supra*) that the two point binding substrates induce a distorted square planar geometry upon binding to catalyst **1**, directly analogous to the bis(aquo) complex **2b**. Inspection of the crystal structure reveals that the malonate diester moiety forms a boat upon binding the Cu atom and induces a slight distortion in the olefin backbone (Fig. 3). The malonate phenyl group is distorted out of the plane of the olefin and away from the t-Bu substituent proximal to it on the ligand. This presents the convex face to attack by nucleophile, a prediction consistent with the observed sense of induction in these systems. We speculate that bulky substituents are required to force the nucleophile into a distorted approach trajectory, analogous to the same effect first observed by Heathcock in carbonyl addition reactions [21].

Aldol additions to bidentate substrates

The high degree of organization afforded by bidentate substrates ultimately led us to consider two-point

binding substrates for activation in Mukaiyama aldol reactions. By analogy, significant facial discrimination should be observed upon binding 1,2-dicarbonyls as well as 2-alkoxy aldehydes to bis(oxazoline)Cu complexes (**11** and **12**; Scheme 9).



Scheme 9

Initial investigations revealed that benzyloxyacetaldehyde forms a well defined complex with catalyst **1a** leading to selective aldol reaction with silylketene acetal **8**, providing the adduct in 91% enantiomer excess and excellent chemical yield [22]. However, the same reaction conducted with [Cu(*S*,*S*)-Ph-pybox]$(SbF_6)_2$ is even more selective, with enantioselectivities typically between 95% and 99% and excellent chemical yields (Eqn 13). Diastereoselectivities are excellent when (*Z*)silylketene acetals are used in this reaction. The substrate catalyst complex, characterized by X-Ray crystallography (Fig. 4), illustrates why such high selectivities are observed in this reaction and correctly predicts the observed stereochemistry. A square pyramidal geometry at Cu is supported by ESR studies and double stereodifferentiating reactions suggesting the same is true for the complex in solution.

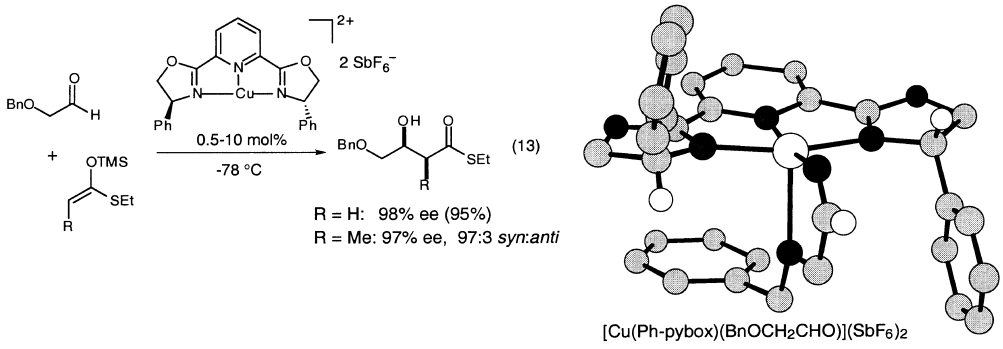
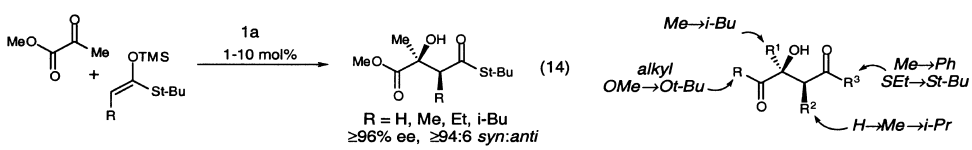


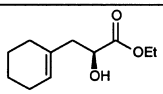
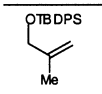
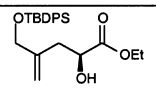
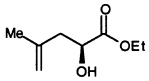
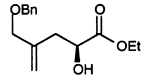
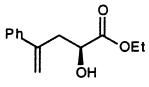
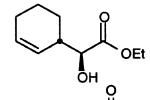
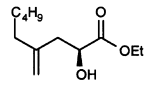
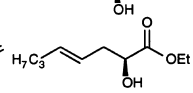
Fig. 4 X-ray structure of catalyst substrate complex (counterions not shown).

Interestingly, slight deviations away from this substrate lead to lower or even complete lack of selectivities, including a siloxyacetaldehyde (55% enantiomer excess), β-benzyloxypropionaldehyde, benzaldehyde and hydrocinnamaldehyde (all racemic). The strict requirements for a 5-membered ring coordination to the carbonyl substrate next directed us to investigate 1,2-dicarbonyls such as glyoxylate and pyruvate esters. Quite unexpectedly, glyoxylate esters provided little or no selectivity in aldol reactions, in direct contrast to the success we had utilizing bis(oxazoline)Sn(II) complexes in this aldol reaction [23] as well as the Cu catalyzed ene reaction of these substrates (*vide infra*). In contrast, pyruvate esters proved to be excellent substrates for this class of catalysts with **1a** affording uniformly high enantioselectivities and excellent diastereoselectivities, largely insensitive to enolsilane geometry (Eqn 14, Scheme 10) [24]. The products formed in all cases possess the *syn* relative stereochemistry, making this reaction complementary to the Sn(II) pybox catalyzed pyruvate aldol which affords the *anti* aldol adducts in high selectivities.



Scheme 10

Table 1 Catalyzed enantioselective ene reactions between ethyl glyoxylate and representative olefins.

olefin	product	cat (mol%)	T,°C	yield,%	% ee	olefin	product	cat (mol%)	T,°C	yield,%	% ee
		**2b** (1) **3a** (10)	0	90 99	97 (*S*) 87 (*R*)			**2b** (1) **3a** (10)	25	72 85	96 (*S*) 91 (*R*)
		**2b** (1) **3a** (10)	0	83 92	96 (*S*) 92 (*R*)			**2b** (10) **3a** (2)	25	62 88	98 (*S*) 92 (*R*)
		**2b** (1) **3a** (10)	0	97 99	93 (*S*) 89 (*R*)			**1b** (10) **3a** (10)	0	95 70	98 (*S*) 94 (*R*)
		**2b** (1) **3a** (10)	25	89 81	96 (*S*) 91 (*R*)			**1b** (10)	25	96	98 (*S*)

2b: [Cu((*S*,*S*)-*t*-Bu-box)(H_2O)](SbF_6)$_2$; **3a**: [Cu((*S*,*S*)-Ph-box)](OTf)$_2$; **1b**: [Cu((*S*,*S*)-*t*-Bu-box)](SbF_6)$_2$

The glyoxylate ene reaction [25]

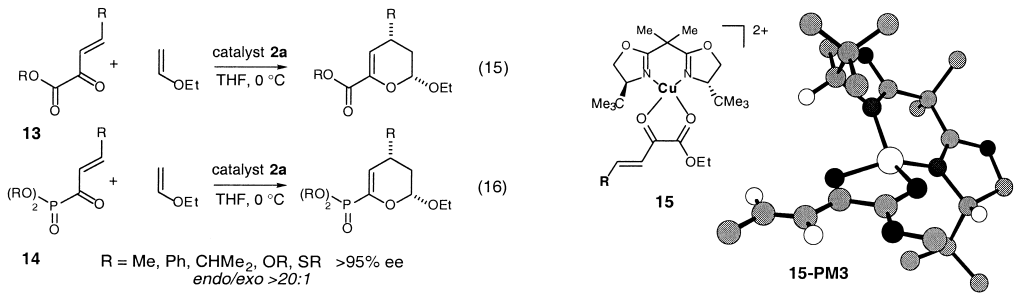
The success of dicarbonyls in the aldol reaction catalyzed by these complexes prompted us to investigate the Lewis acid catalyzed ene reaction with glyoxylate esters (Table 1). These ene reactions exhibit exceptional scope and enantioselectivities. Counterion selection is again critical. At temperatures below –50 °C, no turnover is observed in these reactions; however, this system is quite well-behaved at 0 °C. It is noteworthy that terminal olefins such as 1-hexene readily react under these conditions, marking the first time these olefins had been used in asymmetric carbonyl ene reactions. Enantio- and diastereoselectivities are uniformly high. In fact, this reaction is quite tolerant of hydroxylic functionality, allowing the use of the bench stable aquo complex **2b** as precatalyst in this reaction. The optimal catalyst in this series, [Cu((*S*,*S*)-*t*-Bu-box)(H_2O)$_2$](SbF_6)$_2$ (**2b**) affords product whose absolute stereochemistry is easily rationalized invoking complex **11** as a model. We have also noted a turnover in asymmetric induction when the [Cu((*S*,*S*)-Ph-box)](OTf)$_2$ (**3a**) complex is employed. This reversal in asymmetric induction has also been noted in the hetero Diels–Alder reaction (*vide infra*) and has been discussed in detail elsewhere [7].

Hetero Diels–Alder reactions

Bis(oxazoline) Cu(II) complexes catalyze inverse electron demand hetero Diels–Alder reactions of β,γ-unsaturated α-keto esters **13** and α,β-unsaturated acyl phosphonates **14** with enol ethers (Eqs 15–16, Scheme 11) [5,26]. Circumstantial evidence suggests that the vicinal ketone and ester (phosphono or carboalkoxy) functionalities chelate to the metal center as illustrated in **15**, activating the heterodiene for cycloaddition. Uniformly good levels of diastereo- and enantioselectivity are realized using both [Cu((*S*,*S*)-*t*-Bu-box)(H_2O)$_2$](OTf)$_2$ complex **2a** and [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes **3**; however, complexes **2a** and **3** deliver opposite product anti-podes. The sense of asymmetric induction for **2a** is consistent with the model proposed for the Diels–Alder reaction (through the intermediacy of activated complex **15**), but the reversal in enantiofacial bias for **3** is not easily rationalized [7,27]. As with the conjugate addition reactions described above, the dominance of the LUMO(diene)–HOMO(dienophile) secondary orbital interaction in the *endo* transition state effectively controls the relative stereochemistry. The use of the solid, air stable [Cu((*S*,*S*)-*t*-Bu-box)(H_2O)$_2$](OTf)$_2$ complex **2a** (in conjunction with 3 Å molecular sieves) at 0 °C provides a measure of experimental convenience.

CONCLUSIONS

While the substrate 'chelation requirement' is an apparent limitation for a given family of reactions, our studies have confirmed that 'cross-reaction generality' of [Cu((*S*,*S*)-*t*-Bu-box)](X)$_2$ complexes **1** and **2** has been exceptional. For reactions as diverse as the Diels–Alder and hetero Diels–Alder reactions, aldol addition, and Michael reactions, the enantioselection conferred on these reactions has been unprecedented. As an added benefit, the absolute stereochemistry of the products of these processes



Scheme 11

may be unambiguously interpreted on the basis of simple chelation models that have been developed with the aid of crystallographic, spectroscopic, and chemical methods. Efforts to extend the general utility of these enantioselective processes to other reactions and substrates are ongoing.

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