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Reversal in Enantioselectivity of *tert*-Butyl Versus Phenyl-Substituted Bis(oxazoline) Copper(II) Catalyzed Hetero Diels-Alder and Ene Reactions. Crystallographic and Mechanistic Studies

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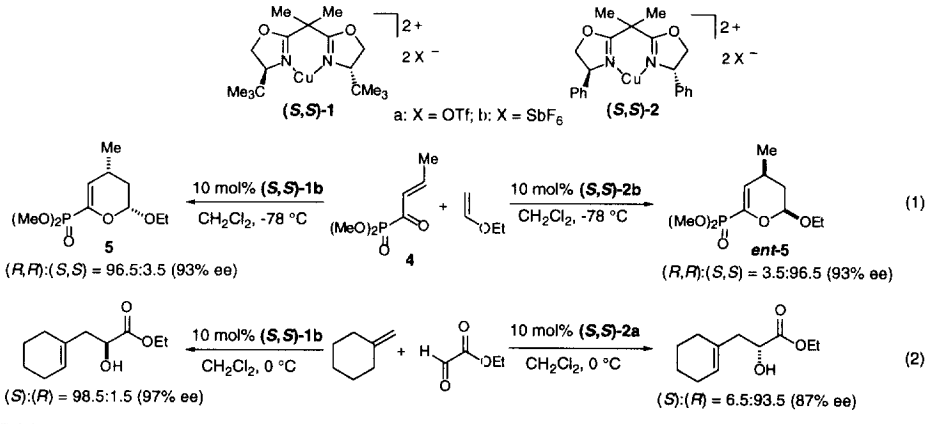
Abstract: X-Ray crystal structures of the Cu[(*S,S*)-*tert*-Bu-bis(oxazoline)]$(H_2O)_2(SbF_6)_2$ (**6**), Cu[(*S,S*)-Ph-bis(oxazoline)]$(H_2O)_2(SbF_6)_2$ (**7**), and Cu[(*S,S*)-*iso*-Pr-bis(oxazoline)]$(H_2O)_2(SbF_6)_2$ (**8**) complexes are presented. Implications of the structural details are considered in the context of the opposite enantiofacial biases conferred by complexes Cu[(*S,S*)-*tert*-Bu-bis(oxazoline)]$(X)_2$ (**1**, X = OTf or SbF_6) and Cu[(*S,S*)-Ph-bis(oxazoline)]$(X)_2$ (**2**) in hetero Diels-Alder and glyoxylate ene reactions. Structural and mechanistic studies suggest that a change in geometry at the metal center is not necessarily responsible for the reversal in enantioselectivity.

Understanding the factors that control π-facial selectivity in enantioselective reactions is a fundamental aspect of asymmetric synthesis. Our laboratory has been concerned with the systematic development of Cu(II) bis(oxazoline) (box) and pyridyl-bis(oxazoline) (pybox) complexes as chiral Lewis acids capable of catalyzing a broad range of enantioselective carbon-carbon bond constructions.[1] To this end, recent reports have documented highly enantioselective Diels-Alder, hetero Diels-Alder, aldol, and glyoxylate ene reactions.[2] Reports from other laboratories also support the notion that these catalysts are broadly applicable.[3] In the course of our investigations we have noted an unexpected turnover in selectivity for certain reactions in which the sole variable that changes is the pendant substituent of the oxazoline ring (eq 1 and 2). A similar phenomenon was first reported by Jørgensen and coworkers in 1995.[4] The absence of a straightforward explanation for the fact that both product antipodes are accessible from a single enantiomeric ligand series warranted further investigation. Herein we report our observations on this reversal in selectivity and experimental efforts to rationalize its occurrence.



Cu(II)bis(oxazoline) complexes (***S,S*)-1** and (***S,S*)-2** catalyze the hetero Diels-Alder reaction of crotonyl phosphonate **4** and ethyl vinyl ether in high yield and diastereoselectivity, with the enantiomeric excess of the product dependent on the oxazoline ring substituent (eq 1). While dihydropyran **5** is obtained in 93% ee employing either *tert*-butyl-substituted (***S,S*)-1b** or phenyl-substituted (***S,S*)-2b**, the derived adducts are enantiomeric. The use of Cu[(*S,S*)-*iso*-Pr-bis(oxazoline)]$(SbF_6)_2$ ((***S,S*)-3b**) affords a product whose enantiomeric purity (39% ee (*S,S*)) is intermediate to those obtained with (***S,S*)-1b** and (***S,S*)-2b**. The same

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trend is observed in the catalyzed ene reaction of methylene cyclohexane and ethyl glyoxylate: (*S,S*)-**1b** and (*S,S*)-**2a** both deliver the product in high, but opposite, enantioselectivity, while (*S,S*)-**3b** affords an adduct of intermediate (36% ee, *S*) enantiomeric excess (eq 2).[2j]

We have accumulated evidence that the stereochemical course of enantioselective reactions catalyzed by complexes (*S,S*)-**1a** and (*S,S*)-**1b** is accounted for by the intermediacy of a distorted square planar bis(oxazoline) Cu(II)•substrate complex. For the realization of high enantioselectivity, the substrate undergoing activation must be capable of bidentate coordination to the chiral Lewis acid. Experimental support for this model is derived from X-ray crystallographic studies of the catalysts,[5] double stereodifferentiating experiments,[2a] EPR spectroscopy,[2i] and semiempirical calculations.[6] The stereoregular behavior exhibited by **1** in a broad range of reactions that employ chelating substrates lends further credence to this analysis. In contrast, the source of asymmetric induction for reactions catalyzed by **2** had not been probed in any detail. Accordingly, structural and mechanistic studies were initiated.

With the goal of understanding the coordination chemistry of the Cu(II) center in complexes **1**-**3**, a X-ray crystallographic study of the hydrated versions of these complexes was undertaken. The results of that study, summarized in Figure 1, reveal a structural trend that is relevant to the experimental results summarized above. In *tert*-butyl-substituted bis(aquo) complex **6**, the Cu(II) center is characterized by a distorted square planar geometry.[5] The distortion of the ligated water molecules is away from the oxazoline substituents an average of +33.3°. The water ligands of the analogous isopropyl-substituted bis(aquo) complex **8** display a similar distortion from square planarity, but the magnitude of the tilt is significantly smaller: an average of +7.0°. This change suggests that the origin of distortion observed for **6** is steric, not electronic, in nature. Such distortions are well-precedented in the chemistry of copper(II).[7] Finally, phenyl substituted bis(aquo) complex **7** also exhibits noticeable distortion from square planarity; however, in this case the water molecules tilt *toward* the oxazoline substituents an average of -9.3°. This distortion is independent of the identity of the counterion, as the triflate-derived complex exhibits a similar deviation from square planarity.[2j]

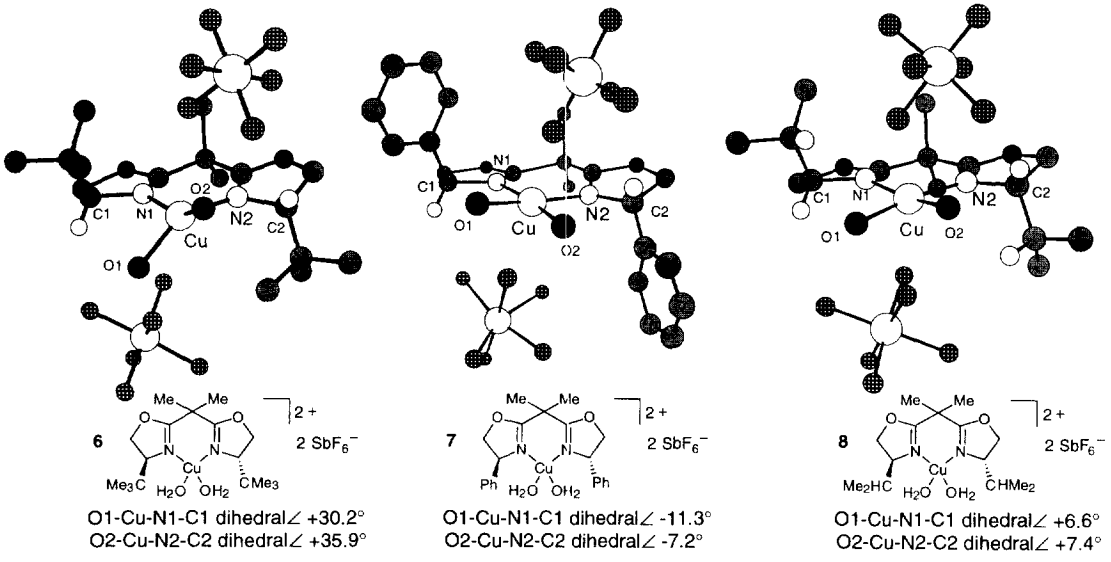


Figure 1. X-ray crystal structures of Cu[bis(oxazoline)$(H_2O)_2$]$(SbF_6)_2$ complexes.

To rationalize the stereochemical outcome of the reactions at hand, it is important to consider not only the structure of the substrate-catalyst complex, but also the interaction of the heterodienophile (or enophile) with that binary complex. To this end, a number of enol ethers were surveyed in hetero Diels-Alder reactions with crotonyl phosphonate **4** (eq 3). The high *endo* selectivity obtained for the reactions of vinyl ethers and **4** catalyzed by (*S,S*)-**2b** is particularly interesting, since a tetrahedral metal center geometry predicts debilitating

steric interactions ($R^1 \leftrightarrow R^2$) in the *endo* transition state if the enol ether conformation is *s-trans*. Experimental and computational work of Houk and coworkers suggests that the *s-trans* conformer is favored in the transition state of such cycloaddition reactions.[8] The fact that good *endo* selectivity is still observed, even for *tert*-butyl vinyl ether, is circumstantial evidence against a transition structure possessing a tetrahedral metal center. This line of analysis can be extended to the glyoxylate ene reaction, since **(*S*,*S*)-2a** is a highly *endo* selective catalyst with the sterically demanding enophile cyclohexene (*endo*:*exo* 95:5, 94% ee). While a tetrahedral copper(II) center seems unlikely for these cases, other geometries are not excluded by the experimental evidence.

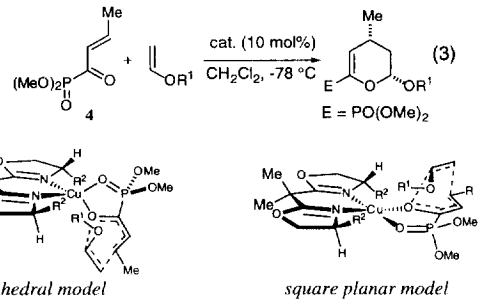


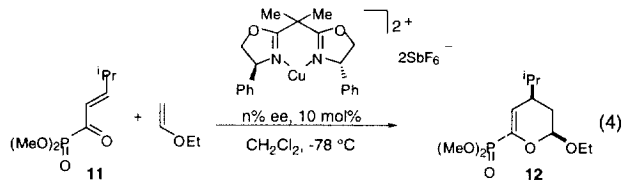
Table 1. Effect of the Enol Ether Alkyl Group in the Catalyzed Hetero Diels-Alder Reaction (eq 3)

product	catalyst	yield	*endo*/*exo*[a]	%ee[a]
9: R^1 = Me	(*S*,*S*)-**1b**	nd	70:1	85
***ent*-9**	(*S*,*S*)-**2b**	95	>99:1	86
5: R^1 = Et	(*S*,*S*)-**1b**	84	69:1	93
***ent*-5**	(*S*,*S*)-**2b**	100	>99:1	93
10: R^1 = ^{t}Bu	(*S*,*S*)-**1b**	35	1.3:1	66 (80)[b]
	(*S*,*S*)-**2b**	100	10:1	2 (55)[b]

[a] Determined by capillary GLC or chiral HPLC. [b] Numbers in parentheses refer to %ee of the *exo* diastereomer.

In an attempt to experimentally determine the contribution of electronic effects[9] to the enantioselectivity reversal, *para*-X-Ph-bis(oxazoline) ligands of varying electronic character were tested; however, no significant differences in enantioselectivity were observed in the hetero Diels-Alder reaction (X = Cl, 89% ee; X = H, 93% ee; X = OMe, 93% ee). Despite the fact that an unambiguous electronic effect was not present, it is important to note the precedent for stereoselective processes in which dipole-dipole and Van der Waals attractions are implicated but do not vary significantly with the π-donor capability of the phenyl group.[10] The present study does not rule out such interactions.

The manifestation of nonlinear effects in asymmetric catalysis can have important consequences for the elucidation of reaction mechanism.[11] The enantiomeric excess of the adduct dihydropyran for the hetero Diels-Alder reaction between acyl phosphonate **11** and ethyl vinyl ether was monitored as a function of enantiomeric composition of the catalyst (eq 4). The results display a linear relationship between the enantiomeric excess of the catalyst and that of the product, thereby suggesting that neither catalyst aggregation nor dimer formation is present. Nonlinear effects are similarly absent in the catalyzed glyoxylate ene reaction; however, the successful isolation of crystals of Cu((*S*,*S*)-Ph-box)$_2$(OTf)$_2$ demonstrates that catalyst sequestration by way of 2:1 ligand:metal complexation is feasible, but not kinetically significant under the reaction conditions.[12] The lack of nonlinear effects in this investigation should be contrasted with other systems employing divalent transition metal bis(oxazoline) and bis(imine) complexes in which substantial asymmetric amplification was reported.[13]



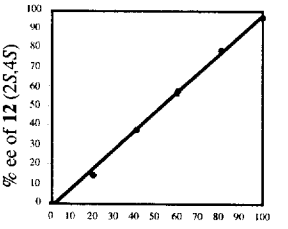


Figure 2. Enantiomeric excess of **12** as a function of catalyst enantiomeric excess.

Consistent with previous findings, Cu(II)box complexes exhibit a favorable temperature-enantioselectivity profile for the hetero Diels-Alder and ene reactions (-78 °C ≤ T ≤ 25 °C).[14] Eyring plots for hetero Diels-Alder reactions catalyzed by (*S*,*S*)-**1a** and (*S*,*S*)-**2a** (eq 1) both show a linear dependence of ln(% major enantiomer/% minor enantiomer) *versus* reciprocal temperature, indicating that only two diastereomeric transition states are operative in these reactions.[15] Thus, if the reversal in selectivity for (*S*,*S*)-**2** results from a new metal geometry,

that geometry must react to the complete exclusion of all others, even at 25 °C. Since **(*S*,*S*)-2b** shows a *reduced* propensity to deviate from square planarity relative to **(*S*,*S*)-1b** (*vide supra*), this scenario seems unlikely.[16] Casting further doubt on that notion are EPR studies performed with complex **(*S*,*S*)-2b** in the presence and absence of crotonyl phosphonate **4**. Those spectral studies correlate well with other EPR spectra obtained for square planar or square pyramidal Cu(box) and Cu(pybox) complexes.

In summary, the present investigation has employed crystallographic and chemical techniques to investigate the cause of a turnover in stereochemistry common to two enantioselective catalytic reactions. Further studies to understand this interesting phenomenon are underway and will be reported in due course.

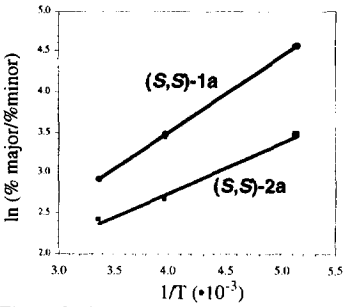


Figure 3. Eyring plots for the hetero Diels-Alder reaction (eq 1) catalyzed by **(*S*,*S*)-1a** and **(*S*,*S*)-2a**.

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