

On the Intermediates in Chiral Bis(oxazoline)copper(II)-Catalyzed Enantioselective Reactions—Experimental and Theoretical Investigations

Jacob Thorhauge, Mark Roberson, Rita G. Hazell, and Karl Anker Jørgensen*^[a]

Abstract: The intermediates in the chiral bis(oxazoline)copper(II)-catalyzed reactions have been investigated by means of experimental and theoretical investigations. It is shown that the absolute configuration of the hetero-Diels–Alder adduct obtained from the reaction of ethyl glyoxylate with 1,3-cyclohexadiene in the presence of the chiral bis(phenyloxazoline)copper(II) is dependent on the solvent. In this case, a linear relationship between the enantiomeric excess (*ee*) and the dielectric constant of the solvent was observed. However, the enantiomeric excess for the adduct obtained with the chiral bis(*tert*-butyloxazoline)copper(II) complex is independent of the solvent. The addition of different coordinating solvents to the chiral catalysts was investigated and no effect on the enantiose-

lectivity of the reaction was observed. A series of chiral bis(*tert*-butyloxazoline)-, bis(phenyloxazoline)-, and bis(indane-oxazoline)copper(II) complexes has been prepared and characterized by X-ray analysis, and the similarity between the structures is discussed. For comparison, two related chiral bis(*tert*-butyloxazoline)- and bis(phenyloxazoline)zinc(II) complexes were also prepared and characterized. A series of chiral bis(oxazoline)copper(II)–substrate (the substrate being glyoxal or methyl glyoxylate) complexes was investigated by means of ab initio calculations. Calculation of the total energy of

the optimized structure of 17-, 19-, and 21-electron bis(oxazoline)copper(II)–substrate complexes give the 17-electron complex as the most stable and the most reactive complex, while the 21-electron complex is less stable and also much less reactive. The optimized structures of both the 17-electron bis(*tert*-butyloxazoline)- and bis(phenyloxazoline)copper(II)–substrate complexes show that the plane of the substrate molecule is twisted by $\approx 40\text{--}45^\circ$ out of the bis(oxazoline)copper(II) plane, in agreement with the X-ray structures. On the basis of the experimental results, X-ray structures, and ab initio calculations, the structure of the intermediate(s) and reactivity of the chiral bis(oxazoline)copper(II)–substrate complexes are discussed.

Keywords: ab initio calculations • asymmetric catalysis • bis(oxazolines) • copper • intermediates

Introduction

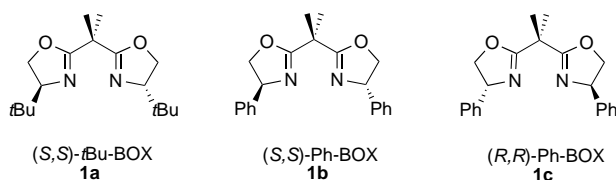
The development of enantioselective reactions catalyzed by chiral Lewis acid complexes for the synthesis of optically active compounds has been under very intense development in recent years.^[1] A variety of new reactions have been found with this concept by applying main group and transition metal salts coordinated to chiral ligands containing “hard” or “soft” heteroatoms.

Compared to the numerous reports dealing with the synthetic developments that use chiral Lewis acids as the catalyst, the number of mechanistic studies of these reactions has been limited. However, the understanding of catalytic

intermediate structures and enantioselective reactions from a mechanistic point of view are of fundamental importance for the further development of versatile and improved chiral catalysts and, hopefully, the possibility to prepare tailor-made chiral catalysts for any given reaction.

This paper will focus on the intermediates in the chiral bis(oxazoline)copper(II)-catalyzed reactions.^[2] The bis(oxazoline) (BOX) ligand was first introduced in 1990 by the group of Masamune et al.^[3a] This was followed shortly after by Evans et al.,^[3b] Corey et al.,^[3c] and the group of Pfaltz.^[3d] The combination of chiral BOX ligands and Lewis acids has been used extensively as enantioselective catalysts for many different reactions, such as aldol,^[4] Diels–Alder,^[3c, 5] 1,3-dipolar cycloaddition,^[6] cyclopropanation,^[3a,b,d, 7] allylic substitution,^[8] allylation and addition,^[9] aziridination,^[10] hetero-Diels–Alder,^[2d, 11] carbonyl-ene,^[11a, 12] Friedel–Crafts,^[13] Friedel–Crafts alkylation,^[14] homoaldol,^[15] δ -lactone formation,^[16] Mannich,^[17] aza-Henry,^[18] and Claisen rearrangement^[19] reactions. The majority of these reactions use the *tert*-butyl-substituted ligand (*S,S*)-*t*Bu-BOX (**1a**), which has often been

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found to be superior in combination with copper(II) salts relative to the (S,S)-Ph-BOX (**1b**) and (R,R)-Ph-BOX ligands (**1c**).

In 1995 we observed the unexpected result that the $[\text{Cu}^{\text{II}}\{(S,S)\text{-}t\text{Bu-BOX}}]$ and $[\text{Cu}^{\text{II}}\{(R,R)\text{-Ph-BOX}}]$ catalysts induced the same absolute configuration in the product for the hetero-Diels–Alder reaction of α -dicarbonyl compounds.^[11a] Since then several investigations in which the (S,S)-tBu-BOX and (R,R)-Ph-BOX ligands in combination with a copper(II) salt have been applied as the catalyst have shown the same type of reversals.^[11b,d,f-k, 12a,c,d, 13a, 14a, 16, 19, 20a] The reversal is most often observed when α -dicarbonyl compounds are used as the substrates; however, a few examples of similar observations with other substrate types have also been observed.^[11j, 20a, 21]

To account for the same absolute configuration observed in reactions catalyzed by the $[\text{Cu}^{\text{II}}\{(S,S)\text{-}t\text{Bu-BOX}}]$ and $[\text{Cu}^{\text{II}}\{(R,R)\text{-Ph-BOX}}]$ complexes, a square-planar intermediate **2** was postulated for the former catalyst, while a tetrahedral intermediate **3** could account for the results obtained by the latter catalyst.^[11a] The proposed structures of these two intermediates **2** and **3** are shown in Figure 1 with methyl glyoxylate as the substrate. These intermediates both have the same face available for approach, namely the *si* face of the carbonyl functionality.

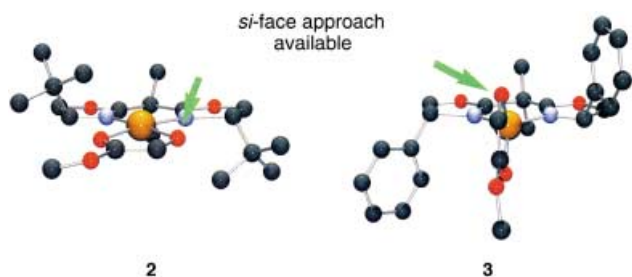


Figure 1. Previously proposed structures for the square-planar intermediate **2** and the tetrahedral intermediate **3**.

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Much effort has been expended to obtain information about the structure of the intermediates in the chiral $[\text{Cu}^{\text{II}}\text{(BOX)}]$ -catalyzed reactions. Several X-ray structures of molecules, such as water, halides, substrates, and substrate-like compounds, coordinated to the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ catalyst support a distorted square-planar intermediate for reactions catalyzed by these complexes.^[11k, 12d, 22]

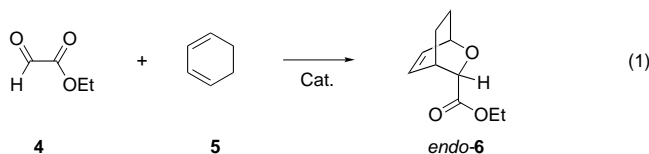
The proposed change in structure especially of the $[\text{Cu}^{\text{II}}\text{(Ph-BOX)}]$ intermediate from a distorted square-planar to a tetrahedral intermediate has resulted in some controversy.^[11j, 22b] Recently Evans et al. suggested that there is more evidence for a mechanism in which π stabilization of the productlike transition state is responsible for the reversal.^[11j]

The chiral $[\text{Cu}^{\text{II}}\text{(BOX)}(\text{substrate})]$ intermediates in these reactions, such as **2** and **3**, are 17-electron d^9 systems and represent a delicate problem, especially with respect to theoretical calculations. Furthermore, NMR studies are also prevented because of the paramagnetic nature of copper(II). Previously, the only serious attempt to perform calculations on the BOX–Cu^{II} system involved molecular mechanics.^[23] Although the CLFSE/MM study by Davies et al. reproduces and predicts X-ray structures of the BOX–copper(II) complexes very well, the MM parameters were adjusted to mimic the experimental X-ray structures, and thus do not provide much more insight than that provided by the original X-ray structures.

This paper presents an experimental and theoretical investigation of the reactions and intermediates of chiral $[\text{Cu}^{\text{II}}\text{(BOX)}]$ -catalyzed transformations. It will be shown that the enantioselectivity can be very dependent on the solvent. Furthermore, a series of X-ray structural determinations of $[\text{Cu}^{\text{II}}\{(S,S)\text{-}t\text{Bu-BOX}}]$, $[\text{Cu}^{\text{II}}\{(S,S)\text{-Ph-BOX}}]$, and $[\text{Cu}^{\text{II}}\{(S,S)\text{-indane-BOX}}]$ salts followed by quantum chemical calculations will give fundamental insight into the structural and electronic properties of the chiral structures of $[\text{Cu}^{\text{II}}\text{(BOX)}]$ intermediates.

Results and Discussion

As a starting point, we studied the hetero-Diels–Alder reaction of ethyl glyoxylate **4** with 1,3-cyclohexadiene **5** [Reaction (1) in Scheme 1]. This investigation was stimulated



Scheme 1.

by our previous unexplained observation^[11a,b] that the reaction of **4** with **5** in CH_2Cl_2 as the solvent in the presence of $[\text{Cu}^{\text{II}}\{(S,S)\text{-}t\text{Bu-BOX}}]$ and $[\text{Cu}^{\text{II}}\{(R,R)\text{-Ph-BOX}}]$ gave *endo*-**6** that has (1*R*,3*S*,4*S*) as the absolute configuration of the major enantiomer, whereas *endo*-**6** with the opposite absolute configuration [(1*S*,3*R*,4*R*)] was obtained as the major enantiomer for the reaction catalyzed by $[\text{Cu}^{\text{II}}\{(R,R)\text{-Ph-BOX}}]$ in

MeNO₂ as the solvent. This prompted us to investigate the hetero-Diels–Alder reaction of **4** with **5** catalyzed by [Cu^{II}[(*S,S*)-Ph-BOX]] and [Cu^{II}[(*S,S*)-*t*Bu-BOX]] in different solvents to determine the absolute configuration (enantiomeric excess, *ee*) of *endo*-**6** as a function of the dielectric constant of the solvent. The results of these investigations are given in Table 1.

Table 1. Hetero-Diels–Alder reaction of ethyl glyoxylate (**4**) with 1,3-cyclohexadiene (**5**) catalyzed by [Cu^{II}[(*S,S*)-Ph-BOX]] and [Cu^{II}[(*S,S*)-*t*Bu-BOX]] in different solvents (dielectric constants).^[a]

| Entry | Solvent | Dielectric constant ^[24] | [Cu ^{II} [(<i>S,S</i>)-Ph-BOX]] <i>ee</i> (%) | [Cu ^{II} [(<i>S,S</i>)- <i>t</i> Bu-BOX]] <i>ee</i> (%) |
|-------|---------------------------------|-------------------------------------|--|--|
| 1 | CDCl ₃ | 4.80 | –79 | 97 |
| 2 | CHCl ₃ | 4.89 | –78 | 97 |
| 3 | THF | 7.47 | –47 | 99 |
| 4 | CH ₂ Cl ₂ | 9.08 | –59 | 97 |
| 5 | EtNO ₂ | 28.96 | 11 | 97 |
| 6 | MeCN | 36.00 | 60 | – |

[a] Negative sign indicates (1*S*,2*R*,4*R*) as the predominant enantiomer.

To our surprise, a (linear) relationship between the enantiomeric excess of the hetero-Diels–Alder adduct *endo*-**6** and the dielectric constant^[24] of the solvent was found when [Cu[(*S,S*)-Ph-BOX]](OTf)₂ was used as the catalyst. It appears also from the results in Table 1 that all the reactions of **4** with **5** catalyzed by [Cu[(*S,S*)-*t*Bu-BOX]](OTf)₂ in the different solvents gave the same high enantiomeric excess (>97% *ee*) of *endo*-**6** [(1*R*,3*S*,4*S*)]. For the relationship between the dielectric constant of the solvent and the enantiomeric excess of *endo*-**6**, it was found that solvents with a low dielectric constant of ≈5 (CHCl₃ and CH₂Cl₂) gave *endo*-**6** in ≈75% *ee* with a (1*S*,3*R*,4*R*) configuration, while solvents that have a dielectric constant of ≈29 (EtNO₂) gave a nearly racemic mixture of *endo*-**6**. When the reaction was performed in a solvent with a dielectric constant of 36 (MeCN), the absolute configuration of *endo*-**6** was (1*R*,3*S*,4*S*) with 60% *ee*. These results indicate that the solvent has a great influence on the structure of the intermediate in reactions induced by [Cu^{II}(Ph-BOX)]. There is, to our knowledge, no theoretical basis for the apparent linear relationship observed between the dielectric constant and enantioselectivity catalyzed by [Cu^{II}[(*S,S*)-Ph-BOX]]. We initially expected that this was caused by the coordination of the solvent to the reaction intermediates (vide infra).

The catalyst is formed by mixing the chiral BOX ligand and the copper(II) salt followed by addition of the substrate to the solution. The substrate is activated by coordination to the chiral [Cu^{II}(BOX)] complex. The substrate-coordinated complex with two anions is a 21-electron complex (copper(II) = d⁹), therefore, the first anion will probably readily dissociate to give a 19-electron complex. Dissociation of the second anion produces the four-coordinate 17-electron [Cu^{II}(BOX)-(substrate)] species. Coordination of a solvent molecule to the latter complex might then give the 19-, or, less likely the 21-electron complex by coordination of two solvent molecules to copper(II). Desimoni et al. have observed that coordinating auxiliaries can not only change, but also reverse, the enantio-

induction in hetero-Diels–Alder reactions catalyzed by chiral [Mg^{II}(BOX)] complexes.^[20] In order to test if a direct coordination of solvent molecules to the [Cu^{II}[(*R,R*)-Ph-BOX](substrate)] intermediate is responsible for the change in absolute configuration of the product, we performed a series of addition experiments. In these experiments H₂O and MeCN were added as auxiliary ligands to both [Cu^{II}[(*S,S*)-

*t*Bu-BOX]] and [Cu^{II}[(*R,R*)-Ph-BOX]] complexes, which were then applied as catalysts to the hetero-Diels–Alder reaction of **4** with **5** (Scheme 1). The results in Figure 2 show the enantioselectivity of *endo*-**6** as a function of H₂O or MeCN equivalents added. It appears that the addition of up to ten equivalents of the coordinating molecules has no effect on the enantioselectivity of the reaction. We therefore propose that the change in enantioselectivity shown in Table 1 is caused by either 1) a subtle difference in the 17-electron [Cu^{II}(Ph-BOX)(substrate)] structure because of the dielectric properties of the solvent, or 2) competition from a slower but much more abundant 19-electron [Cu^{II}(Ph-BOX)] solvent–solvent complex, which directs the formation of the opposite enantiomer compared to the 17-electron [Cu^{II}-(Ph-BOX)(solvent)] complex.

In an attempt to throw some further light onto the intermediate of these chiral [Cu^{II}(BOX)] reactions, a series

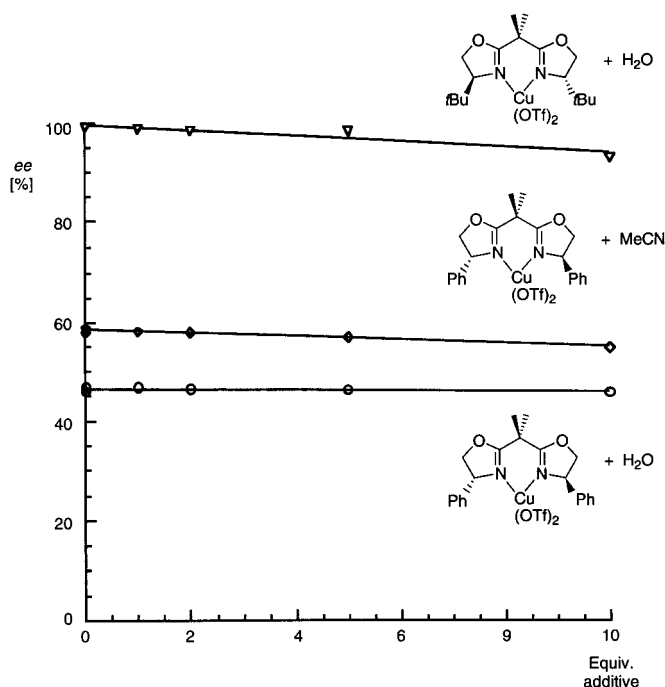


Figure 2. Enantiomeric excess of *endo*-**6** from the reaction of **4** with **5** as a function of additive relative to the [Cu(OTf)₂]((*R,R*)-Ph-BOX)] and [Cu(OTf)₂]((*S,S*)-*t*Bu-BOX)] catalysts. The reactions with H₂O as additive were performed in THF as the solvent. The reactions with MeCN as additive were preformed with CH₂Cl₂ as the solvent.

of theoretical investigation has been performed. As the semiempirical calculation models, such as AM1, MNDO, ZINDO, and PM3, proved to be too crude to describe the geometry at the copper atom, the calculations were carried out by means of restricted open-shell Hartree Fock (ROHF) calculations. These calculations were performed with the Jaguar electronic structure program with the LACVP basis set.^[25] This basis is valence double-zeta for the light atoms and uses an effective core potential for the copper atom.

For the investigation of the 21-, 19-, and 17-electron complexes of $[\text{Cu}^{\text{II}}(\text{BOX})(\text{substrate})]$ species we initially chose the intermediate formed by the coordination of methyl glyoxylate to $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}]$, the 17-electron complex, **7a**.

The geometry of **7a** has been optimized (Figure 3) and some representative bond lengths are given in Table 2. The total energy of **7a** is calculated to be -1454.4139 au. The Cu–N and Cu–O bond lengths are similar to those found in related

Table 2. Calculated energies and some representative bond lengths and angles in intermediates **7a–c**.

| | 7a | 7b | 7c |
|----------------------------------|--------------|--------------|--------------|
| energy [au] | -1454.4139 | -1586.3211 | -1718.2176 |
| ΔE [kcal] ^[a] | 0.0 | 15.6 | 37.8 |
| Cu–N1 [Å] | 1.978 | 2.040 | 2.098 |
| Cu–N2 [Å] | 1.969 | 1.993 | 2.051 |
| Cu–O1 [Å] | 2.060 | 2.041 | 2.081 |
| Cu–O2 [Å] | 2.227 | 2.711 | 3.229 |
| C–O1 [Å] | 1.241 | 1.237 | 1.231 |
| C–O2 [Å] | 1.217 | 1.209 | 1.204 |
| C–C [Å] | 1.521 | 1.515 | 1.511 |
| Cu–N3 [Å] | – | 2.178 | 2.305 |
| Cu–N4 [Å] | – | – | 2.176 |
| twist angle [°] ^[b] | 40.4 | – | – |
| LUMO(C=O2) | -6.45 eV | -5.41 eV | -4.67 eV |

[a] The energy is calculated relative to **7a** + one/two free MeCN. Total energy of optimized structure of MeCN: -131.9321 au. [b] Average twist out of square-planar.^[26]

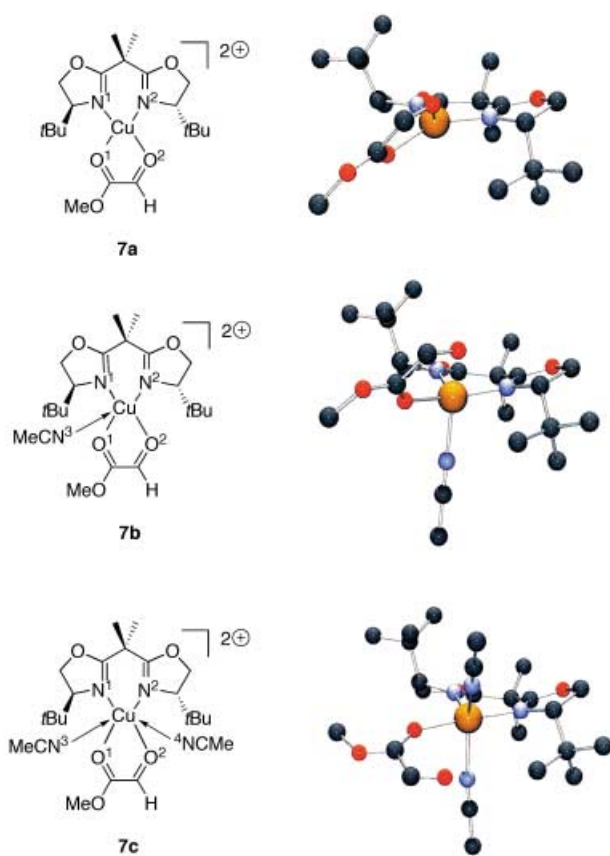


Figure 3. Calculated (ab initio) minimum energy geometries for 17-, 19-, and 21-electron species with $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}(\text{methyl glyoxylate})]$ coordinated to 0, 1, and 2 MeCN molecules.

complexes determined by X-ray analysis.^[5b, 11k, 22] The C–O1 and C–O2 bond lengths are only slightly distorted by coordination to $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}]$. An important factor for the reactivity of **7a** is the energy of the LUMO orbital, which is the orbital responsible for the interaction with the HOMO of the incoming electron-rich reagent. For complex **7a**, this LUMO energy has been calculated to be -6.45 eV. To investigate the stability of the different electron-count com-

plexes we have used MeCN rather than anions as the coordinating ligands, because MeCN gives the same qualitative result, but avoids problems in comparing calculation results from complexes with different charges.

For the optimized structure of the 19-electron complex (**7b**, Figure 3), some results are presented in Table 2. It is notable that **7b** is both less stable by 15.6 kcal mol^{−1}, and that the methyl glyoxylate is less reactive, as the LUMO is 1.04 eV higher in energy than that found for **7a**. The structural data of the bis(oxazoline)copper(II) fragment in **7b** is very similar to the data in **7a**. An important and interesting change for the coordination of methyl glyoxylate to the chiral catalyst is found on going from the 17-electron to the 19-electron complex; in **7a** the Cu–O2 bond length (O2 is the reacting carbonyl oxygen atom) is calculated to be 2.227 Å, while this bond length in **7b** increases to 2.711 Å. This change in Cu–O2 bond length shows that the carbonyl functionality of methyl glyoxylate is less coordinated to the Lewis acid in the latter complex, which accounts for the higher LUMO energy and thus less reactive complex **7b** compared to **7a**.

The results in Table 2 for the 21-electron complex **7c** show that this is the least stable complex (37.8 kcal mol^{−1} higher in energy than **7a**) and that the methyl glyoxylate in this complex is the least reactive of the three intermediates considered. The most important structural change in **7c** compared to the two other complexes is the Cu–O2 bond length, which has been calculated to be 3.229 Å; namely, the reacting carbonyl functionality in methyl glyoxylate in this complex is not coordinated to the copper(II) center (which actually makes it a formal 19-electron complex). These theoretical results show that both the most stable and most reactive species of the $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}(\text{methyl glyoxylate})]$ complexes considered is the four-coordinate 17-electron species **7a** without any coordinating solvent molecules (or anions). This result is in agreement with the absence of effect from auxiliary ligands in the experimental results (vide supra).

The 17-electron species **7a** contains an unpaired electron. However, this complex shows, according to our knowledge, no

radical character in the catalytic reactions. This indicates that the single-occupied molecular orbital (SOMO) is located in the complex in such a way that it does not interact with the substrate/reagent during the reaction. The SOMO orbital has been calculated to be exclusively located at the copper center (coefficient at copper: 0.934) in the plane of the BOX ligand and the substrate as a d_{xy} orbital (Figure 4). The LUMO of **7a** schematically shown in Figure 4 is, as expected, the π^* orbital of the glyoxylate located at the carbonyl functionalities, perpendicular to the plane of the molecule, and set up for interaction with the reagent. This orbital has its largest amplitude at the carbon atom of the aldehyde functionality.

The X-ray crystal structures of chiral bis(oxazoline)copper(II) complexes used so far to explain the stereochemical outcome of the catalysis all typically have two water molecules coordinated to the metal. These crystal structures have one, or both, of the anions placed in what would be the axial position(s) of the square-planar or twisted square-planar structure. The presence of the anions probably has a considerable effect on the resulting X-ray crystal structure. The X-ray structures of the 21-electron complexes, $[\text{Cu}(\text{Ph-BOX})(\text{H}_2\text{O})_2](\text{OTf})_2$ and $[\text{Cu}(\text{Ph-BOX})(\text{H}_2\text{O})_2](\text{SbF}_6)_2$, which are often used as models for the reacting intermediate, show an octahedral geometry around the copper center (or a square-planar structure when the anions are omitted).^[5b, 22c]

In Figure 5 the square-pyramidal $[\text{Cu}^{\text{II}}(\text{tBu-BOX})-(\text{H}_2\text{O})_2](\text{OTf})_2$ complex (**8**) is shown as an example of a 19-electron complex. Some characteristic structure values are given in Table 3.

In an attempt to obtain further information about the structure of four-coordinate 17-electron chiral bis(oxazoline)-copper(II) intermediates, we prepared crystals of $[\text{CuX}_2(\text{tBu-BOX})]$, $[\text{CuX}_2(\text{Ph-BOX})]$, and $[\text{CuX}_2(\text{indane-BOX})]$ complexes **9a–f** (Reactions (2)–(4) in Scheme 2). Figure 6 shows

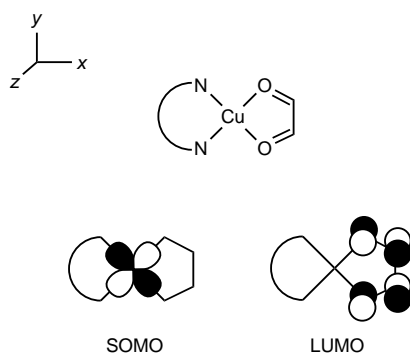


Figure 4. Schematic representation of the calculated SOMO and LUMO of **7a**.

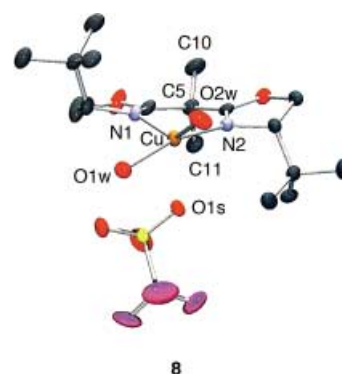
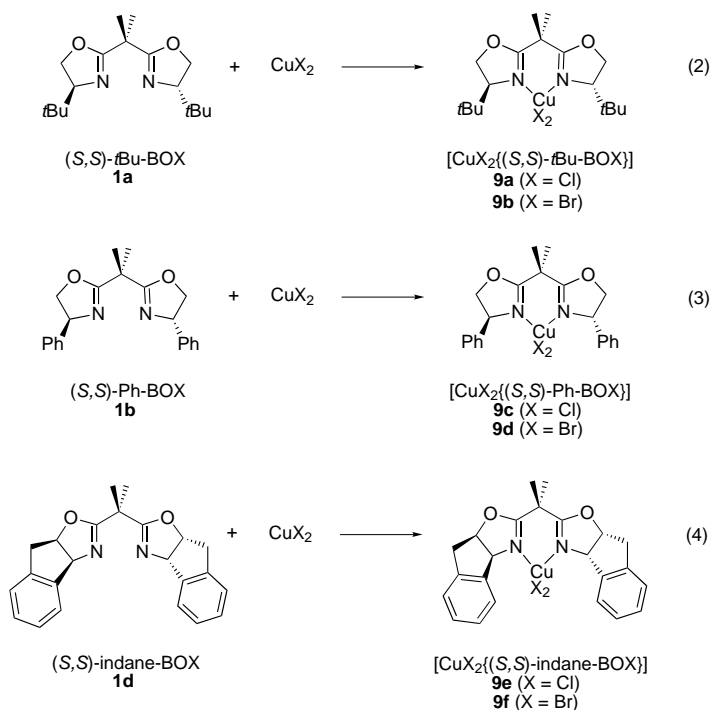


Figure 5. X-ray structure of the $[\text{Cu}(\text{OTf})_2\{(\text{S},\text{S})\text{-tBu-BOX}\}(\text{H}_2\text{O})_2]$ complex **8**. One non-coordinating triflate is omitted for clarity.

Table 3. Some structural data for the chiral $[\text{Cu}(\text{OTf})_2\{\text{bis}(\text{oxazoline})\}(\text{H}_2\text{O})_2]$ complex **8**, the chiral $[\text{CuX}_2\{\text{bis}(\text{oxazoline})\}]$ complexes **9a–f**, and the chiral $[\text{ZnCl}_2\{\text{bis}(\text{oxazoline})\}]$ complexes **10a, b**.

| | $\angle \text{C10-C5-Cu-X2}$ [$^\circ$] ^[a] | $\angle \text{C11-C5-Cu-X1}$ [$^\circ$] ^[a] | Cu-N1 [Å] | Cu-N2 [Å] | Cu-X1 [Å] | Cu-X2 [Å] |
|---------------------------------|--|--|-----------|-----------|-----------|-----------|
| 8 ^[b] (X = O) | 45.5 | 22.6 | 1.961 | 1.929 | 1.959 | 1.979 |
| 9a (X = Cl) | 44.6 | 44.6 | 1.983 | 1.983 | 2.232 | 2.232 |
| 9b (X = Br) | 49.6 | 49.6 | 1.979 | 1.979 | 2.365 | 2.365 |
| 9c (X = Cl) | 45.1 | 51.6 | 1.974 | 1.988 | 2.239 | 2.214 |
| 9d (X = Br) | 46.5 | 56.0 | 1.968 | 1.980 | 2.365 | 2.344 |
| 9e (X = Cl) | 45.9 | 41.0 | 1.997 | 1.992 | 2.223 | 2.234 |
| 9e twin | 41.8 | 49.7 | 1.959 | 1.997 | 2.255 | 2.240 |
| 9f (X = Br) | 44.4 | 52.9 | 1.963 | 1.966 | 2.361 | 2.369 |
| 9f twin | 42.8 | 47.7 | 1.965 | 1.982 | 2.368 | 2.363 |
| 10a (X = Cl) | 59.1 | 67.3 | 2.068 | 2.042 | 2.227 | 2.232 |
| 10b (X = Cl) | 73.3 | 77.5 | 2.032 | 2.022 | 2.228 | 2.203 |

[a] Written as 90° – dihedral angle as earlier studies have kept the square-planar case as 0° .^[26] [b] Cu–O (OTf) distance = 2.472 Å.



Scheme 2.

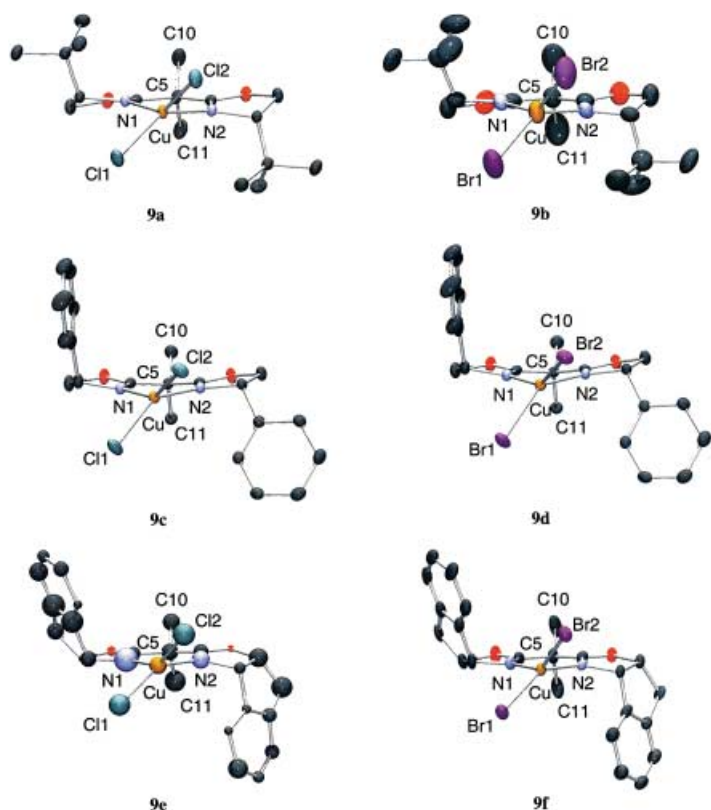


Figure 6. X-ray structures of $[\text{CuX}_2\{(\text{S},\text{S})\text{-}t\text{Bu-BOX}\}]$ complexes **9a, b**, $[\text{CuX}_2\{(\text{S},\text{S})\text{-Ph-BOX}\}]$ complexes **9c, d**, and $[\text{CuX}_2\{(\text{S},\text{S})\text{-indane-BOX}\}]$ complexes **9e, f**. Non-coordinating crystal solvent molecules are omitted for clarity when present.

the solved X-ray structure of these complexes and some representative structural data are given in Table 3.

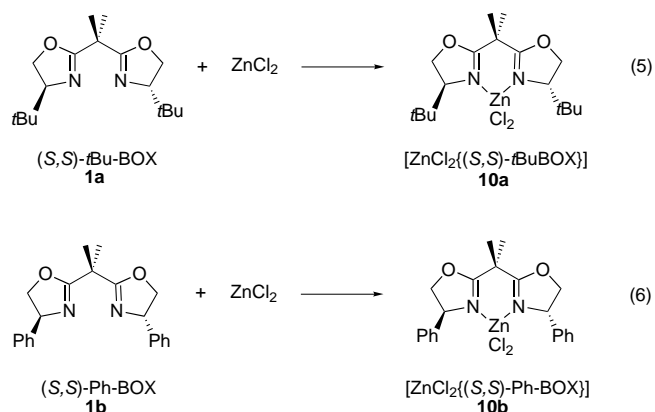
The six chiral complexes $[\text{CuX}_2\{\text{bis(oxazoline)}\}]$ ($\text{X} = \text{Cl}, \text{Br}$) **9a–f** all have one trend in common: the angle between the X1-Cu-X2 plane and the bis(oxazoline)copper(II) plane is very similar in all the complexes. It lies between 41° and 56° ; in the ideal square-planar case this angle would be 0° .^[26, 27] The different orientation of the phenyl substituents in **9c, d** is also notable; they are oriented $\approx 90^\circ$ relative to each other with the “left-phenyl substituent” perpendicular and the “right-phenyl substituent” parallel to the halogen ions that coordinate to the copper(II) center. At the present stage of investigations, we cannot explain the reason for, or the importance of, the difference in the orientation of the phenyl substituents in **9c, d**. It could be subtle effects from crystal packing, or it could be a more important general trend as that, for example, observed by Seebach et al. for the Ti–TADDOL complexes.^[28] At least it could indicate that the structure of the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ complex is more flexible than that of the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})(\text{substrate})]$ complex. It appears from Table 3 that essential bond lengths around the copper(II) center are similar in all six complexes **9a–f**.

To investigate the influence of the structure of the metal complex on the enantioselectivity, the hetero-Diels–Alder reaction of **4** with **5** was catalyzed by $[\text{Zn}(\text{OTf})_2\{(\text{S},\text{S})\text{-Ph-BOX}\}]$ and $[\text{Zn}(\text{OTf})_2\{(\text{S},\text{S})\text{-}t\text{Bu-BOX}\}]$. The $[\text{Zn}^{\text{II}}(\text{BOX})\text{-(substrate)}]$ complexes are most likely to be tetrahedral as they represent four-coordinate 18-electron complexes. The

hetero-Diels–Alder reaction catalyzed by $[\text{Zn}(\text{OTf})_2\{(\text{S},\text{S})\text{-}t\text{Bu-BOX}\}]$ in CH_2Cl_2 gave less than 5% conversion to *endo*-**6**, and only 33% *ee* compared to 97% *ee* in the copper-catalyzed reaction. When $[\text{Zn}(\text{OTf})_2\{(\text{S},\text{S})\text{-Ph-BOX}\}]$ was used as the catalyst, the other enantiomer of *endo*-**6** was obtained in 34% *ee*; when the copper catalyst was used 58% *ee* was obtained. If the intermediate bis(oxazoline)-zinc(II) complexes are tetrahedral, then it is highly remarkable that the enantio-directing effect of the ligands is similar to that found for copper complexes.

The two crystals $[\text{Zn}^{\text{II}}\text{Cl}_2(t\text{Bu-BOX})]$ (**10a**) and $[\text{Zn}^{\text{II}}\text{Cl}_2(\text{Ph-BOX})]$ (**10b**), (Reactions (5) and (6) in Scheme 3) were prepared in order to compare them to the copper(II) crystals **9a–f**. The X-ray structures of **10a, b** are shown in Figure 7 and some representative structural data are given in Table 3.

As expected, the structure of the two chiral zinc(II) complexes **10a, b** are more close to a tetrahedral geometry at the metal than the corresponding chiral copper(II) com-



Scheme 3.

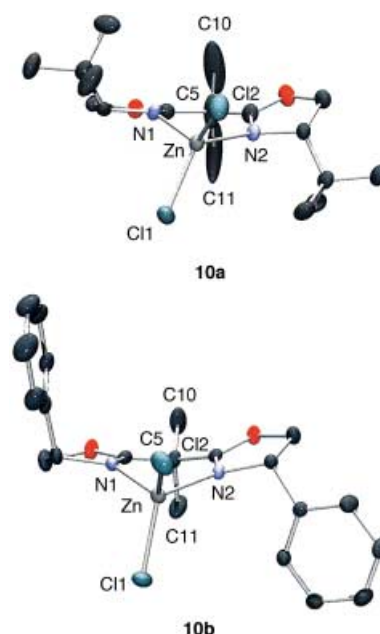


Figure 7. X-ray structures of $[\text{ZnCl}_2\{(\text{S},\text{S})\text{-}t\text{Bu-BOX}\}]$ complex **10a** and $[\text{ZnCl}_2\{(\text{S},\text{S})\text{-Ph-BOX}\}]$ complex **10b**.

plexes. The bis(oxazoline) ligands are for both structures more bend than the corresponding copper structures **9a–d**. The average twist angle out of square planar^[26] is 63.2° for **10a** and 75.4° for **10b**. The lower average twist angle out of square-planar for **10a** indicates that the structure is less flexible than that of **10b**. For **10b** the phenyls are arranged perpendicular to each other as in **9c, d**.

It appears from the experimental results that the [Cu^{II}(Ph-BOX)(substrate)] complex, in particular, shows a flexible geometry, as, for example, the absolute configuration (enantiomeric excess) of the hetero-Diels–Alder reaction is dependent on the dielectric constant of the solvent. In an attempt to obtain further information about the structure of the chiral bis(oxazoline)copper(II)–substrate intermediates we have calculated the change in energy for the [Cu^{II}(Ph-BOX)(glyoxal)] and [Cu^{II}(*t*Bu-BOX)(glyoxal)] complexes as a function of the rotation of the glyoxal functionality relative to the chiral [Cu^{II}(BOX)] complex as outlined in **11** (Figure 8). The calculated change in energy as a function of angle (θ) between the plane of the glyoxal–copper(II) and the plane of the bis(oxazoline)copper(II) is shown in Figure 8.^[26] The calculations are performed with constrained C₂ symmetry.

The curves in Figure 8 show that the [Cu^{II}(Ph-BOX)(glyoxal)] intermediate, with respect to rotation of the glyoxal fragment relative to the bis(oxazoline)copper(II) plane, is much more flexible than the [Cu^{II}(*t*Bu-BOX)(glyoxal)] intermediate. The minimum in energy calculated for the [Cu^{II}(Ph-BOX)(glyoxal)] complex (−1487.3360 au) is at $\theta = 40^\circ$ and the energy required for rotation of the glyoxal to the square-planar intermediate is 4 kcal mol^{−1}, while the energy required for the tetrahedral intermediate is 5 kcal mol^{−1}, relative to the minimum energy. For the [Cu^{II}(*t*Bu-BOX)(glyoxal)] intermediate, the square-planar and tetrahedral intermediate structures are 11 kcal mol^{−1} and 9 kcal mol^{−1} higher in energy, respectively, than the energy-minimum-calculated structure (−1340.5312 au) at $\theta = 45^\circ$. The orientation of the glyoxal fragment relative to the bis(oxazoline)copper(II) plane in these calculated minimum-energy geometries for the [Cu^{II}(Ph-BOX)(glyoxal)] and [Cu^{II}(*t*Bu-BOX)(glyoxal)] in-

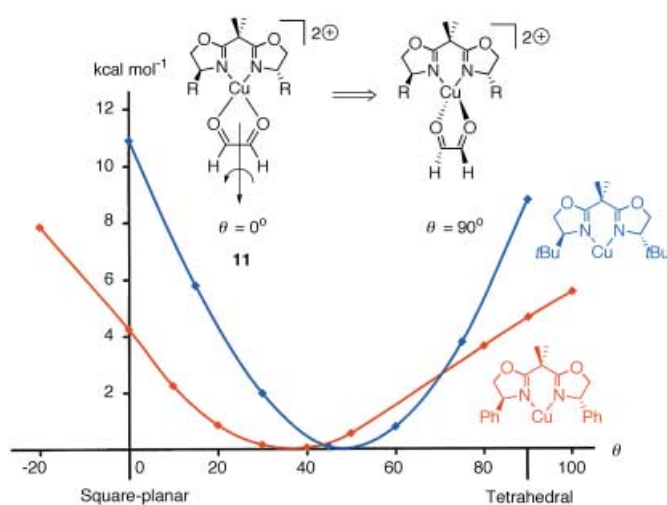


Figure 8. Calculated energies for [Cu^{II}(Ph-BOX)(glyoxal)] (red curve) and [Cu^{II}(*t*Bu-BOX)(glyoxal)] (blue curve) as a function of the twist angle out of square-planar (θ).^[26]

intermediates is in agreement with the X-ray structures of [CuX₂(*t*Bu-BOX)] complexes **9a, b** and [CuX₂(Ph-BOX)] complexes **9c, d**.

When viewing the calculated 17-electron [Cu^{II}[(*S,S*)-*t*Bu-BOX](methyl glyoxylate)] complex **7a** in a space-filling model, we observe that the *re* face of the reacting aldehyde is perfectly shielded from attack (A in Figure 9). When the

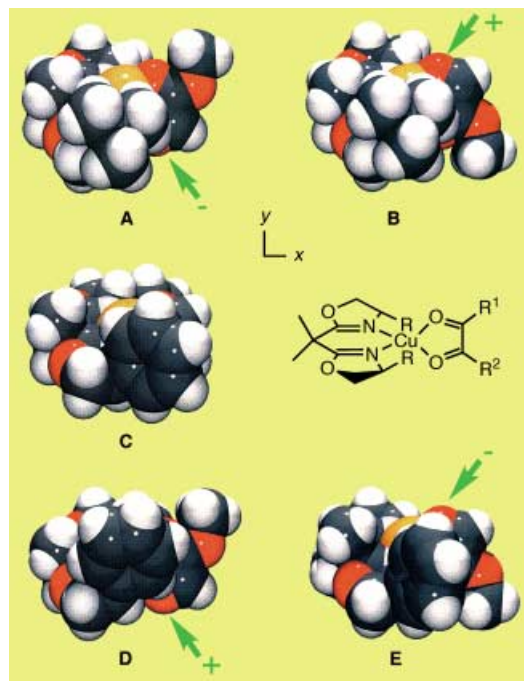


Figure 9. A, B: Calculated structure of [Cu^{II}[(*S,S*)-*t*Bu-BOX](methyl glyoxylate)] (**7a**). C: calculated structure of [Cu^{II}(Ph-BOX)(glyoxal)] at $\theta = 40^\circ$ (**12**). D, E: Crystal structure [CuCl₂[(*S,S*)-Ph-BOX]] (**9c**), without anions but with the methyl glyoxylate fragment from **7a** superimposed. The arrows show the reacting carbonyl functionality. The signs indicate + for an unshielded carbonyl functionality and − for a shielded carbonyl functionality.

model is rotated by 180° around the *x* axis, the *si* face of the aldehyde is visible and is available for approach of the reagent (B in Figure 9). The face selectivity, based on the X-ray structures of **9a** and **b** and the calculated energy minimum of the [Cu^{II}[(*S,S*)-*t*Bu-BOX](methyl glyoxylate)] complex **7a**, is in agreement with the experimental results.

In structure C in Figure 9 the calculated minimum structure of [Cu^{II}[(*S,S*)-Ph-BOX](glyoxal)] (**12**) is viewed in a similar way. With the glyoxyl substrate molecule placed in the right in the *xy* plane, it is completely shielded from both sides (as the calculated complex is C₂ symmetric). This indicates that in order to react, this complex has to undergo some sort of geometrical change. We tried to use the geometrical structure of the Ph-BOX ligand found in the crystal structures of the [Cu^{II}X₂(Ph-BOX)] complexes **9c** and **9d** in combination with the copper-methyl glyoxylate taken from **7a** to investigate whether the carbonyl functionality would be unshielded by the chiral ligand and be able to react. The methyl glyoxylate was placed in the plane defined by the copper and the chlorides in complex **9c**. The aldehyde functionality was placed in the direction of Cl1 in **9c** and the ester in the

direction of the Cl2 in **9c**. Comparison of this combined model (without the chlorides) with the methyl glyoxylate oriented as in A and B in Figure 9 shows that the *re* face of the carbonyl functionality is only partly shielded (D in Figure 9) and that the *si* face is more shielded (E in Figure 9). It can be seen from D and E in Figure 9 that the ester oxygen is completely shielded from both sides so that binding of the methyl glyoxylate in the opposite fashion would lead to no reaction. The intermediate D thus show that it is possible for reagents to approach the *re* face of the carbonyl functionality. The approach to this face in the latter case is opposite to the that found for the $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}(\text{methyl glyoxylate})]$ complex.

Inspection of the chiral substituent in structure **9c** reveals that the two phenyls are not only oriented differently, but they also seem to be positioned pseudoaxially and pseudoequatorially to the left and right, respectively. This observation raises the question as to whether the angle between the chiral substituent and the oxazoline ring is important. In Table 4 the dihedral angles C1-C2-N1-C4 and C9-C8-N2-C6 are reported for all the crystal structures and some of the calculated structures.

If dihedral angles $< 115^\circ$ are taken as pseudoaxial and the dihedral angles $> 115^\circ$ as pseudoequatorial, then an interesting trend can be seen from Table 4. All the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ structures have both *t*Bu substituents in the pseudoaxial position. However, the relaxed non-metal-bound *t*Bu-BOX ligand (**1a**) has both *t*Bu substituents in the relaxed pseudoequatorial position (Figure 10). The structures of the (Ph-BOX)–metal complexes have one phenyl substituent in the

pseudoaxial position and the other phenyl substituent in the pseudoequatorial position. The indane-BOX structures have the benzene rings locked in a pseudoaxial position. This indicates that the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ structures and the $[\text{Cu}^{\text{II}}(\text{indane-BOX})]$ structures are very locked and inflexible, while the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ structures are more flexible because at least one of the phenyl groups is in the relaxed pseudoequatorial position. We believe that the pseudoaxial and pseudoequatorial position of the phenyl substituents in the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ catalyst is of importance for the enantio-induction in these reactions.

Evans et al. have previously suggested that the reversals could be attributed to a π stabilization of the transition state when the Ph-BOX ligand is employed.^[11j] According to Evans et al., the accumulated experimental evidence provides more support for this π stabilization than for a tetrahedral copper intermediate.^[11j] Evans et al. observed changes in the absolute configuration of the hetero-Diels–Alder product formed from crotonyl phosphonate and ethyl vinyl ether when different $[\text{Cu}\{(\text{S,S})\text{-BOX}\}(\text{SbF}_6)_2]$ complexes were employed as catalysts. The *t*Bu-BOX ligand favored the formation of the product with (2*R*,4*R*) configuration in 97% *ee*, but the Ph-BOX, the Bn-BOX, and even the *i*Pr-BOX ligands favor the (2*S*,4*S*) configuration of the product in 93%, 58%, and 39% *ee*, respectively. Since the reversal is observed even with an *i*Pr-BOX ligand, a π stabilization of the transition state clearly cannot be the only reason. In the $[\text{Cu}^{\text{II}}(i\text{Pr-BOX})]$ case, the reason must be a geometrical change of sterical origin.

Based on the intermediates outlined in Figure 9, it is thus possible to account for the change in face selectivity when changing the chiral ligand from *t*Bu-BOX to Ph-BOX in these copper(II)-catalyzed reactions. The intermediate structures also indicate that the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ catalyst should be expected to give higher enantioselectivities relative to the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ catalyst in reactions in which four-coordinate copper(II) intermediates are involved. These predictions are in agreement with the experimental results.

However, it has to be taken into account that the calculations are performed without a solvent and for the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ -catalyzed reactions it has been found that the enantioselectivity and absolute configuration of the product formed can be dependent on the dielectric constant of the solvent (Table 1). Comparing the face selectivity for the intermediates (based on X-ray structures and theoretical calculations) presented in A and B, and D and E (Figure 9), respectively, with the change in enantioselectivity found for the hetero-Diels–Alder reaction in Table 1, a good agreement is found for reactions performed in solvents with a low dielectric constant. Reactions performed in solvents that have a low dielectric constant approach the conditions for which the theoretical conditions are performed.

For reactions catalyzed by $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ in solvents with a high dielectric constant, a change in enantio-induction is found compared to reactions in solvents with a low dielectric constant. For reactions that take place in solvents with a high dielectric constant, the absolute stereochemical outcome of the reaction is the same for the $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-Ph-BOX}\}]$ and $[\text{Cu}^{\text{II}}\{(\text{S,S})\text{-}t\text{Bu-BOX}\}]$ catalysts. The change in intermediate structure for the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ complex when

Table 4. Dihedral angles for the X-ray structures of the chiral bisoxazoline **1a**, the chiral $[\text{Cu}(\text{OTf})_2\{\text{bis}(\text{oxazoline})\}(\text{H}_2\text{O})_2]$ **8**, the chiral $[\text{CuX}_2\{\text{bis}(\text{oxazoline})\}]$ complexes **9a–f**, the chiral $[\text{ZnCl}_2\{\text{bis}(\text{oxazoline})\}]$ complexes **10a, b**, the calculated structure **7a**, and the calculated structure of $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{glyoxal})]$ (**12**) at $\theta = 40^\circ$.

| | $\angle \text{C1-C2-N1-C4 } [^\circ]$ | $\angle \text{C9-C8-N2-C6 } [^\circ]$ |
|---------------------|---------------------------------------|---------------------------------------|
| 1a | 134.7 | 124.9 |
| 7a | 109.2 | 111.3 |
| 8 | 106.1 | 111.5 |
| 9a (X = Cl) | 106.6 | 106.6 |
| 9b (X = Br) | 110.2 | 110.2 |
| 9c (X = Cl) | 105.7 | 119.3 |
| 9d (X = Br) | 106.0 | 118.0 |
| 9e (X = Cl) | 98.7 | 105.5 |
| 9e twin | 97.5 | 103.0 |
| 9f (X = Br) | 104.9 | 99.6 |
| 9f twin | 101.2 | 101.4 |
| 10a (X = Cl) | 127.9 | 113.3 |
| 10b (X = Cl) | 105.2 | 121.8 |
| 12 | 133.5 | 133.5 |

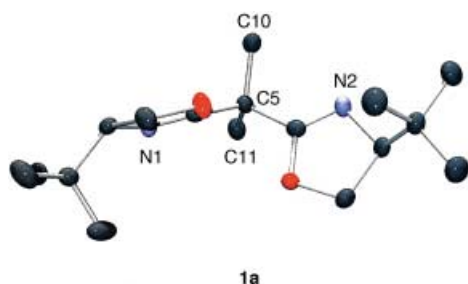


Figure 10. X-ray structure of (S,S)-*t*Bu-BOX **1a**.

changing the solvent is not evident—it can be caused by several factors. The red curve in Figure 8 indicates that the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ intermediate is much more flexible than the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})(\text{substrate})]$ intermediate and that only 4–5 kcal mol^{−1} is necessary to produce a square-planar or the tetrahedral geometry of the intermediate. A change of the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ intermediate towards the distorted square-planar geometry will give rise to the same face selectivity as found for the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ catalyst. The change of intermediate structure can be initiated by subtle differences in the 17-electron $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})(\text{substrate})]$ complex because of the dielectrical properties of the solvent. One reason could be a change in orbital occupation: the 17-electron $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ complex has a number of nearly degenerate orbitals around the SOMO level, and a change in orbital occupation might lead to a system that is more stable towards a more distorted square-planar complex compared to those shown in Figures 6 and 8. Another explanation could be the competition from the slower reaction of a much more abundant 19-electron $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})(\text{solvent})]$ complex, which directs the formation of the opposite enantiomer compared to the 17-electron $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ complex.

Conclusion

Based on experiments, X-ray structures, and theoretical calculations, we believe that the observed reversal in enantioselectivity when changing from the $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})]$ system to the $[\text{Cu}^{\text{II}}(\text{Ph-BOX})]$ system is caused by a geometrical change, mainly of sterical origin. The earlier focus of static square-planar and tetrahedral intermediates should probably be avoided because both the reactive 17-electron $[\text{Cu}^{\text{II}}(t\text{Bu-BOX})(\text{substrate})]$ and $[\text{Cu}^{\text{II}}(\text{Ph-BOX})(\text{substrate})]$ complexes probably exist in conformations right in the middle of the two extremes. Focus should rather be put on the flexibility and dynamics of the ligands in use. This flexibility includes not only the ability to twist between square-planar and tetrahedral extremes, but also the ability of the chiral substituent to rock between pseudoaxial and pseudoequatorial positions.

Experimental Section

General methods: All reactions were carried out under an atmosphere of N₂ using anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. The product was purified by flash chromatography (FC) on Merck silica gel 60 (230–400 mesh). The enantiomeric excess (*ee*) of the product was determined by chiral GC on a Chrompack Chiralsil-Dex CB column.

Materials: 2,2'-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], (*R*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline), (*S*)-2,2'-isopropylidenebis(4-phenyl-2-oxazoline), $[\text{3aR}-[2(3'aR^*,8'aS^*),3'a\beta,8'a\beta]]-(+)-2,2'$ -methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole], 1,3-cyclohexadiene, ZnCl₂, CuCl₂, CuBr₂, and Cu(OTf)₂ were purchased from Sigma-Aldrich. Cu(OTf)₂ was stored under an inert atmosphere and only handled in air for a few minutes before use. Ethyl glyoxylate was prepared by ozonolysis of diethyl maleic acid according to literature procedures and was freshly distilled before use.^[29] The indane-BOX ligand was synthesized from [3aR-

$2(3'aR^*,8'aS^*),3'a\beta,8'a\beta]]-(+)-2,2'$ -methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazole] and iodomethane following a literature procedure.^[30]

General procedure used for the solvent study: In a Schlenk tube, $[\text{Cu}(\text{OTf})_2]$ (36.1 mg, 0.10 mmol) and the bis(oxazoline) ligand (0.105–0.11 mmol) were stirred vigorously under vacuum for 30 min. Solvent (2 mL) was added and the catalyst was stirred for another 30 min. All solvents used in this study gave homogeneous green or pale blue catalyst solutions. Ethyl glyoxylate (0.15 mL, 1.5 mmol) and then 1,3-cyclohexadiene (95 μL , 1.0 mmol) were added to the catalyst solution. The reaction was stirred at room temperature for 18 h and then quenched through a short plug of silica gel with CH₂Cl₂ as the eluent. The solvent was evaporated and the product was checked by ¹H NMR spectroscopy.^[11a] The *ee* of the product was determined by chiral GC on a Chrompack Chiralsil-Dex CB column. The absolute configuration of the product was obtained by comparison with literature data.^[11a]

General procedure used for the additive study: In a Schlenk tube, Cu(OTf)₂ (36.1 mg, 0.10 mmol) and the bis(oxazoline) ligand (0.105–0.11 mmol) were stirred vigorously under vacuum for 30 min. Solvent (2 mL) and additive were added, and the catalyst was stirred for another 30 min. The catalyst solutions used were homogeneous green or pale blue. Ethyl glyoxylate (0.15 mL, 1.5 mmol) and then 1,3-cyclohexadiene (95 μL , 1.0 mmol) were added to the catalyst solution. The reaction was stirred at room temperature for 18 h and then quenched through a short plug of silica gel with CH₂Cl₂ as the eluent. The solvent was evaporated and the product was checked by ¹H NMR spectroscopy.^[11a] The *ee* of the product was determined by chiral GC on a Chrompack Chiralsil-Dex CB column. The absolute configuration of the product was obtained by comparison with literature data.^[11a]

General procedure used for the preparation of crystals: In a Schlenk tube, the metal salt (0.10 mmol) and the bis(oxazoline) ligand (0.10 mmol) were stirred vigorously under vacuum for 30 min. CH₂Cl₂ or THF (1–2 mL) was added, and the catalyst was stirred for another 30 min. The catalyst solution was left under a gentle flow of N₂ for several days until the solvent had evaporated and crystals of sufficient size were produced.

X-ray data: All data were collected on a SIEMENS SMART CCD diffractometer in the narrow-frame omega-scan mode,^[31] with MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) from a graphite monochromator. All but **9b** were collected at 120 K. Structures were solved with SIR97^[32] and refined by the least-squares method with data averaged to preserve differences as a result of anomalous scattering, so that the absolute configuration could be determined.^[33] CCDC-166461–CCDC-166469 and CCDC-171723 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk). Atom numbering might differ from the numbering used in the ORTEP drawings^[34] in Figures 5–7, and 10.

2,2'-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (1a): Orthorhombic, $P2_12_12_1$, $a = 6.4248(4)$, $b = 10.0148(7)$, $c = 27.7(7) \text{ \AA}$, 26315 reflections measured, 7713 unique, 5760 with $I > 3\sigma(I)$ used in the refinement of 379 parameters, $R = 0.028$, $R_w = 0.031$.

2,2'-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]dihydrocopper(II) trifluoromethanesulfonate salt (8): Orthorhombic, $P2_12_12_1$, $a = 9.565(3)$, $b = 12.031(3)$, $c = 25.236(7) \text{ \AA}$, 18635 reflections measured, 5074 unique, 2548 with $I > 3\sigma(I)$ used in the refinement of 199 parameters, $R = 0.030$, $R_w = 0.032$.

2,2'-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]dichlorocopper(II) (9a): Compound **9a** crystallized with one molecule of methylenechloride (solvent). Monoclinic, $C2$, $a = 16.5800(9)$, $b = 9.3408(5)$, $c = 9.5024(5) \text{ \AA}$, 17676 reflections measured, 3486 unique, 3320 with $I > 3\sigma(I)$ used in the refinement of 143 parameters, $R = 0.028$, $R_w = 0.037$.

2,2'-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]dibromo(II)copper (9b): Compound **9b** crystallized with one molecule of THF (solvent). Trigonal, $P3_121$, $a = b = 9.732(6)$, $c = 24.04(2) \text{ \AA}$, 23565 reflections measured at 300 K, 6281 unique, 2022 with $I > 3\sigma(I)$ used to refine 138 parameters in constrained refinement according to Pawley.^[34] Hydrogen atoms on methyl groups allowed a rotational parameter for each group. The THF group was restrained with bond lengths of 1.43(2) \AA for C–O and 1.53(2) \AA for C–C and with a distance of 2.36(3) \AA to the next neighbor. Thermal parameters of tetrahydrofuran were constrained to the TL model.

One occupation parameter was refined for tetrahydrofuran. $R=0.045$, $R_w=0.052$.

2,2'-Isopropylidenebis(4-phenyl-2-oxazoline)dichlorocopper(II) (9c): Orthorhombic, $P2_12_12_1$, $a=8.626(1)$, $b=11.814(2)$, $c=20.382(3)$ Å, 30047 reflections measured, 6162 unique, 5637 with $I>3\sigma(I)$ used in the refinement of 343 parameters. $R=0.020$, $R_w=0.026$.

2,2'-Isopropylidenebis(4-phenyl-2-oxazoline)dibromocopper(II) (9d): Orthorhombic, $P2_12_12_1$, $a=8.7864(4)$, $b=11.9913(5)$, $c=20.2269(9)$ Å, 30778 reflections measured, 6199 unique of which 5534 with $I>3\sigma(I)$ were used to refine 343 parameters, $R=0.018$, $R_w=0.019$.

{3aR-[2(3'aR*,8'aS*),3'aβ,8'aβ]}-(+)-2,2'-methylenebis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole)dichlorocopper(II) (9e): Orthorhombic, $P2_12_12_1$, $a=13.602(3)$, $b=13.761(3)$, $c=23.506(5)$ Å, 34826 reflections measured, 6358 unique, 4220 with $I>3\sigma(I)$ used in the refinement of 248 parameters. Crystals were all poorly diffracting pseudotetragonal twins, and the structure was in itself pseudotetragonal. The reflections from the two twins were overlapped, so the least-squares program was modified to add the intensities of the two contributions. Constraints between thermal parameters of atoms related by the pseudosymmetry had to be applied to obtain reasonable convergence. Only the heavy atoms were allowed anisotropic thermal parameters. $R=0.079$, $R_w=0.085$.

{3aR-[2(3'aR*,8'aS*),3'aβ,8'aβ]}-(+)-2,2'-methylenebis(3a,8a-dihydro-8H-indeno[1,2-d]oxazole)dichlorocopper(II) (9f): Orthorhombic, $P2_12_12_1$, $a=13.711(1)$, $b=13.960(1)$, $c=23.563(2)$ Å, 48517 reflections measured, 13216 unique, of which 10831 with $I>3\sigma(I)$ were used to refine 543 parameters. $R=0.042$, $R_w=0.052$.

2,2'-Isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline]dichlorozinc(II) (10a): Compound **10a** crystallized with one molecule of THF (solvent). Orthorhombic, $P2_12_12_1$, $a=9.183(3)$, $b=11.936(4)$, $c=22.783(8)$ Å, 25887 reflections measured, 7233 unique, 6199 with $I>3\sigma(I)$ were used in the refinement of 281 parameters. The crystals contain molecules of tetrahydrofuran solvent that show large atomic displacement parameters: it is possible that there is disordering. The bridging isopropyl group is disordered and has been modeled with a disordered, isotropic central atom and the methyl groups disordered and refined with anisotropic displacement parameters. $R=0.047$, $R_w=0.060$.

2,2'-Isopropylidenebis(4-phenyl-2-oxazoline)dichlorozinc(II) (10b): Orthorhombic, $P2_12_12_1$, $a=8.642(1)$, $b=11.798(2)$, $c=20.594(3)$ Å, 19257 reflections measured, 5852 unique, 5539 with $I>3\sigma(I)$ used to refine 343 parameters. $R=0.022$, $R_w=0.028$.

Acknowledgement

This work was made possible by a grant from The Danish National Research Foundation.

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Received: September 12, 2001 [F3553]