Quantitative Chirality Analysis of Molecular Subunits of Bis(oxazoline)copper(II) Complexes in Relation to Their Enantioselective Catalytic Activity

Santiago Alvarez,*[a] Sabine Schefzick,[b] Kenny Lipkowitz,[b] and David Avnir*[c]

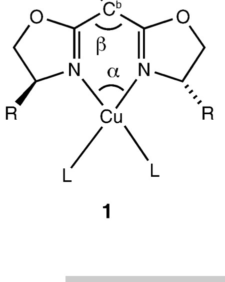
Abstract: The analysis of the quantitative chirality of molecular subunits of spirocyclic bisoxazoline copper complexes was carried out in order to identify the molecular portions most responsible for the chirality of the whole molecule, and therefore also for its catalytic enantioselectivity. It is shown that the smallest fragment that carries the information on molecular chirality contains only a portion of the bidentate bisoxazoline ligands and most atoms of the two monodentate ligands. The structural parameters that are best correlated to the chirality measures of the studied systems are the bond angles at the bridgehead spiro-carbon atom. A prediction is made for an analogous catalyst with potentially high enatioselectivity.

Keywords: chirality · coordination compounds · enantioselectivity · homogeneous catalysis

Introduction

Bis(oxazoline)–Cu^{II} complexes **1** are important enantioselective catalysts.[1,2] The interest in this family has originated in part from the possibility of affecting the chirality through the use of a wide variety of substituents on the basic skeleton of **1**. We recall that, in general, tetracoordinated complexes with two pairs of ligands (connected or not) have a chiral coordination shell if the torsion angle, τ, between the two pairs (see **2**) is not 0 or 90°. Whereas both of these extreme angles belong to the achiral C_{2v} symmetry point group, all τ values in-between lead to the chiral C_2 symmetry point group of the coordination shell. In the copper oxazoline complexes, **1**, there is in fact another possible source of chirality, namely that of the oxazoline ligands themselves.

We have focused recently[3] on the chirality/enantioselectivity relations in the family of spirocyclic bisoxazoline copper complexes (**3**, $n = 1$–4), which had been reported to catalyze a Diels–Alder reaction between acrylimide and cyclopentadiene. In that study we found that the enantiomeric excess (*ee*) of the product changes with n and, by theoretically optimizing the geometry of these compounds, an excellent correlation was found between a quantitative chirality measure—to be defined shortly—of the whole molecule and the *ee*. Yet, since various subunits of **3** have different levels of chirality, it is of interest to try and identify possible correlations between the level of chirality of selected moieties of the catalyst and its enantioselectivity. This, indeed, is the



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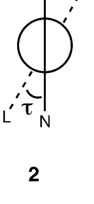

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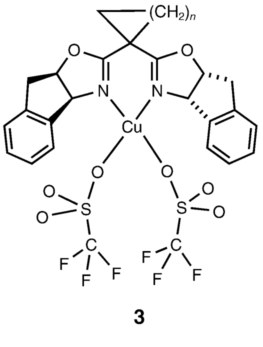

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main aim of this report. Such correlations, if found, may help in the rational design of better catalysts.

The continuous chirality measure (CCM) methodology we employ—see references [4–12] for some of its applications—is a distance function which evaluates of how far a given structure is from being achiral.[13,14] It is a special distance function, in that the reference achiral shape to which that distance is minimal, is unknown a priori, but is searched.

$$S = \frac{\sum_{k=1}^{N} |\boldsymbol{Q}_\mathbf{k} - \boldsymbol{P}_\mathbf{k}|^2}{\sum_{k=1}^{N} |\boldsymbol{Q}_\mathbf{k} - \boldsymbol{Q}_\mathbf{0}|^2} \tag{1}$$

Here, N is the number of atoms in the investigated fragment (or of the whole molecule), $\boldsymbol{Q}_\mathbf{k}$ is the vector of the position of each of these atoms, $\boldsymbol{P}_\mathbf{k}$ is the vector of the positions of each of the N points of the nearest achiral structure, the denominator is a size normalization factor ($\boldsymbol{Q}_0$ is the vector of coordinates of the center of mass of the investigated structure) and the factor of 100 is introduced for convenience.[15] The measure takes values between 0 (achiral molecule) and less than 100; the larger the S, the more chiral the molecule is. In another application of Equation (1), also used in this report, one can select $\boldsymbol{P}_\mathbf{k}$ to be a reference achiral shape which is not necessarily that of the minimal distance.

In the context of this report we mention the application of the CCM approach to hexacoordinate transition metal complexes—many of which are catalytically important as well—which has resulted in some interesting findings. For instance, we were able to generalize the chirality behaviour of a variety of homoleptic, monodentate ML_6 complexes with metaprismatic structures[16] (intermediate between octahedral and trigonal prismatic), and have provided computational evidence that the racemization in such complexes may be slow at room temperature.[17] In another study of the CCM of tris(chelate) complexes[8] it was shown that the chiralities of the first atomic shell (i.e., the metal and its immediate donor atoms) and of the second shell (comprising the spacers between two donor atoms of a bidentate ligand) provide a good estimate for the chirality of the full molecule; and that the chirality of the inner shell is amplified or damped depending on the type of bidentate ligand used. In a study of spin crossover in hexacoordinate complexes,[18] we showed how the chirality of the coordination sphere is strongly correlated to changes in temperature and to the magnetic moment in these systems. Tetracoordinate metal complexes of catalytic relevance were also subjected to the CCM analysis. Thus, in a study of the chirality of tetracoordinate bischelate metal complexes, we have shown that the rigidity of the bidentate ligands imposes a variety of chiral structures, all of which can be found along a strictly well defined distortion route, namely that of the tetrahedral to square planar *twist* interconversion pathway,[9] among which the double stranded helicates were found to be a particular case of this general behaviour.

In the present study we undertake a detailed quantitative analysis of the chirality measures of the family of **3** and address the three following issues: i) What are the structural differences among the members of this family that are responsible for differences in the chirality values of the whole molecules? ii) Which is the smallest common molecular portion that reproduces the trend of the chirality of the full molecules and the correlation with the *ee*? iii) How do structural parameters (bond or torsion angles) affect the chirality measures?

Abstract in Catalan: *Una anàlisi quantitativa de la quiralitat de fragments moleculars en complexos de coure amb bisoxazolines espirocícliques s'ha portat a terme amb L'objectiu d'identificar quins d'aquests fragments són responsables de la quiralitat de la molècula en conjunt i, al capdavall, de la seva enantioselectivitat catalítica. Es mostra que el fragment més petit que emmagatzema la informació sobre la quiralitat molecular conté tan sols una porció dels lligands bisoxazolina i la major part dels àtoms dels dos lligands monodentats. Els paràmetres estructurals que es correlacionen millor amb les mesures de quiralitat dels sistemes estudiats són els angles d'enllaç a L'átom de carboni espirànic. Es fa una predicció d'un nou catalitzador d'aquesta família que hauria de tenir una enantioselectivitat molt elevada.*

Results and Discussion

A relationship between the bite angle of bidentate diphosphine complexes of Pd and Rh catalysts and their enantioselectivity has been reported in several reactions.[19,20] Hence, a starting point for our analysis of complexes **3** is to assume that differences in the N-Cu-N bite angle (α, shown in **1**) might be responsible for their different chirality measures and for the resulting different *ee* values. However, no such correlation was found for **3**. Likewise, no correlation was found for 3 between the chirality value and the torsion angle τ (shown in **2**; τ between 24 and 36°).[9]

Since the only change within the family of compounds **3** is the size of the spiro-cycloalkane, our next choice was to focus on the geometry around the bridgehead carbon (C^b in **1**), as a "wrench" for inducing chirality in remote portions of the molecule. Indeed, the distortive power of the cycloalkane ring is transmitted to the C^b-connected oxazoline rings: As the size of the cycloalkane increases, so does the C-C^b-C bridgehead bond angle within the ring (γ, Table 1). This, in turn, affects both the bridgehead bond angle within the chelate ring, β (in **1**) and the R^2R^3CC torsion angle, δ, between the cycloalkane and the chelate ring. The angles β, γ and δ are seen (Figure 1 and Table 1) to be well correlated to each other but not to α. Even more important is the observation of a good correlation between the geometry around the bridgehead carbon atom and the chirality of the full molecule, S_f (calculated with all non-hydrogen atoms) as shown (for β) in Figure 2. This correlation between β and S_f confirms that the spiro-cycloalkane modulates the chirality

Table 1. Some structural parameters[a] and chirality measures[b] for the theoretically optimized copper(II) bisoxazolines **3** (n=1–4) and **4** and of several fragments.

Compound	τ[c]	α[c]	β[c]	γ[c]	δ[c]	H···CuNN	O···HC	S_f	S_1	S_2	S_b	S_g
2 (n=1)	33	95.0	114.9	58.5	33.6	0.87	1.813	5.81	0.27	7.02	8.11	9.22
2 (n=2)	24	95.3	113.4	88.8	49.5	0.80	1.828	5.59	0.29	8.10	7.61	8.45
2 (n=3)	31	95.8	112.4	106.3	58.1	0.79	1.812	5.46	1.10	7.72	7.55	8.40
2 (n=4)	36	94.9	111.4	112.5	60.4	0.74	1.808	4.92	0.01	4.47	6.47	7.36
4	33	95.1	116.9	0.0	0.0	0.96	1.815	5.98	0.26	7.01	8.25	9.36

[a] All distances in Å, angles in degrees. [b] S_f corresponds to the chirality measure of the full molecule without hydrogen atoms, the other symmetry measures correspond to the fragments defined in Figure 4. [c] The angles α, β, γ and τ are defined in **1** and **2**; δ is the R^2R^3CC torsion angle around the bridgehead carbon atom.

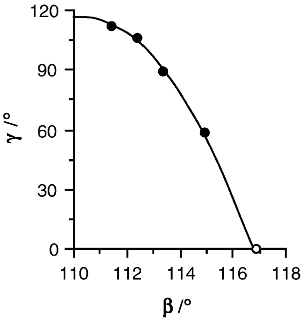


Figure 1. Correlation between the two C-C^b-C bond angles (**1**) at the bridgehead carbon atom in compounds **3** (●) and **4** (○). The line corresponds to a least-squares fitting of the black circles only.

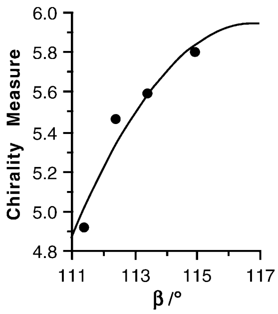
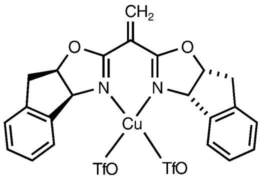


Figure 2. Relationship between the chirality measures of the full molecules **3** (excluding the H atoms) and the bridghead C-C^b-C bond angle within the chelate ring of **1**.



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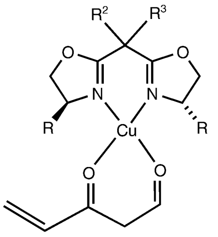

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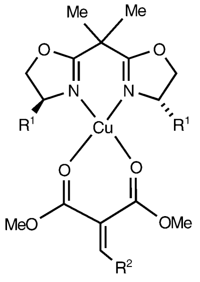


6a: R^1 = *t*Bu
6b: R^1 = Ph

of other portions of the molecule and we will devote some effort below to find out the origin of this effect.

Since the reported correlation between the chirality measures of **3** and the resulting *ee* values[3] indicated an increase in the *ee* with S_f, one can attempt at this point to propose a useful prediction as to other derivatives of **3** which may show high *ee* activity. Focusing on the bridgehead angles, it is seen that higher S_f (and therefore higher *ee*) would require a β angle larger than 115° (Figure 2). What does this mean about the spiro-cycloalkane? Extrapolation of the curve in Figure 1 (fitted to a second order polynomial) predicts $\beta \approx 117°$ and $\gamma = 0°$. The interpretation of this pair of values is straightforward, namely that C^b should be of sp^2 hybridization as would correspond to the smallest possible "spiro-cycloalkane" in the **3** series with n=0 (tantamount to considering the C=CH_2 group as a "two-member" ring). This corresponds to the hypothetical molecule **4**; the geometry of which we had therefore optimized (geometry optimization has been carried out as described in ref. [3]). The results (Table 1) tell us that indeed the value of β for such a compound is practically that expected for γ=0° (Figure 1, white circle) and its calculated molecular chirality (S_f value, Table 1) is higher than for compounds **3**, with a predicted *ee* value of 98%.

Our second goal is to identify the smallest fragment of **3** and **4** that carries the chirality of the full molecule (and therefore is the minimal unit responsible for the *ee* dependence). The strategy we use consists of two elements: First, gradual "shaving" of the molecule from the outer periphery towards the copper atom; and second—for the sake of consistency—determination of the chirality value with respect to a *fixed* reference plane, namely the nearest one found for the full molecule within the pseudotetrahedral symmetry (i.e., τ=90°, C_{2v} symmetry) around the Cu atom; it is the plane perpendicular to the chelate ring, shown in Figure 3.

A full listing of all the fragments of complexes **3** obtained by the shaving procedure is provided as Supporting Information. The most relevant fragments for the subsequent discussion are shown in Figure 4, where only the symbols of those atoms considered for a given chirality measure (S_1, S_2, S_b, or S_g) are shown. Our first finding using this strategy was that removing the spiro-cycloalkane and the phenyl rings in the flaps (Figure 4, S_b) preserves the chirality information, diminishing somewhat the chirality values (Figure 5). Further "shaving" of four carbon atoms and two oxygen atoms (Figure 4, S_g) leaves a fragment which still retains the chirality behaviour of the whole molecule

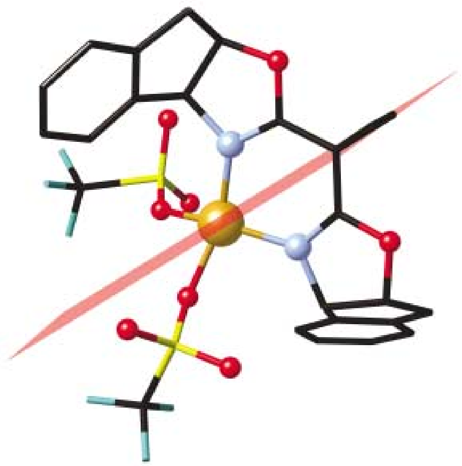


Figure 3. Perspective view of the molecular structure of **3** ($n = 1$) showing the pseudosymmetry reference plane for the chirality measures.

(Figure 5). If further atoms are removed (e.g., the F atoms of the triflate anions, or the C_5 rings of the bisoxazoline flaps), the correlation becomes poor. We have also calculated the chirality measures of the bisoxazoline ligands alone and that of the $Cu(OTf)_2$ moieties, but neither correlates with S_f. We can therefore conclude that the smallest fragment that contains the full molecular chirality information is *g*, shown in Figure 6 in a side view. It follows from Figure 5 that the catalytic enantioselectivity of **3** should be well represented by S_g, and this is nicely seen in Figure 6. To further check these results we have also optimized compound **5**, the analogous of **4** in which the $C{=}CH_2$ bridgehead is substituted by $C{=}O$. The resulting S_f value is plotted in Figure 5 as a function of the corresponding S_b and S_g measures (white symbols) and is seen to fit very well with the behavior of **3** and **4**.

As seen from the above analysis, neither the chiral bisoxazoline ligand, nor the monodentate ligands alone are responsible for the chirality contents of these compounds (hence for their enantioselectivity), but both contribute significantly to the molecular chirality. Interestingly the two triflate residues have a similar conformation for **3** ($n = 1$–3), but a different orientation for **3** ($n = 4$), as shown in Figure 7. Still, the chirality measure seems to take into account these conformational differences.

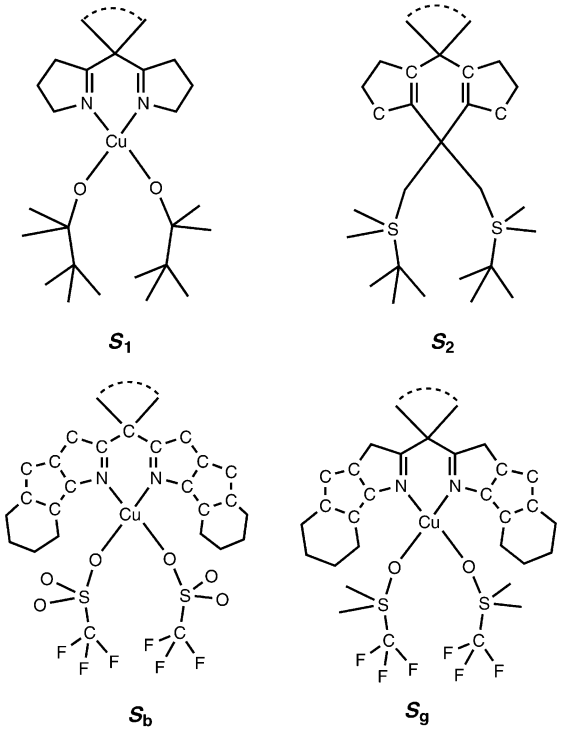


Figure 4. Some fragments of the complexes **3** for which chirality measures were determined. For a given chirality measure (S_1, S_2, S_b, or S_g), only the atoms whose symbols are shown were considered.

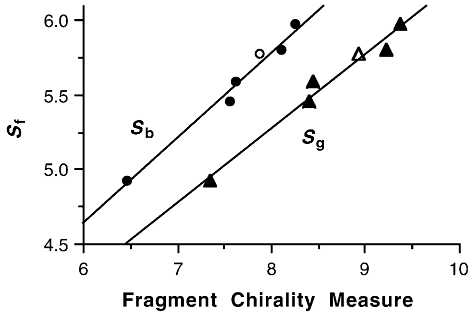


Figure 5. Relationship between the chirality measure of the full molecules of complexes **3** and **4**, and those of their fragments **b** (●) and **g** (▲, see Figure 4 for a description of fragments). The corresponding values for compound **5** (**4** with a $C{=}O$ replacing the $C{=}CH_2$ group at the bridgehead position) are also presented (empty symbols).

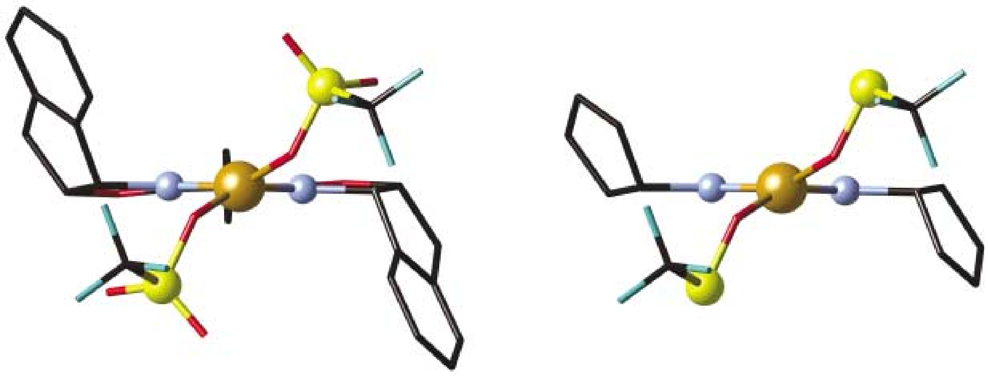


Figure 6. View along the C_2 axis of the optimized structure of complex **4** and of its smallest fragment holding all the chirality information (**g**, Figure 4). Note the helix formed by the C_5 flaps and the triflate ligands.

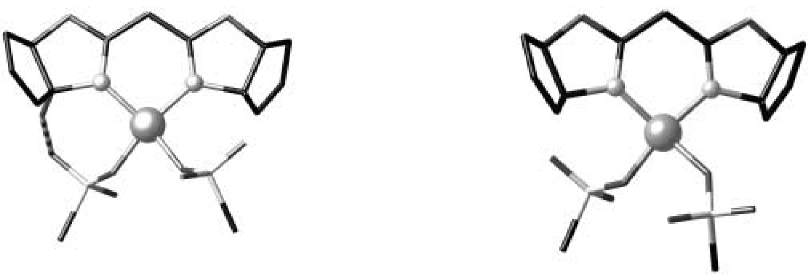


Figure 7. Projection of the basic skeleton of compounds **3** ($n=3$, left) and **3** ($n=4$, right), showing the two different conformations adopted by the triflate ligands. A short O···H distance between the triflate and bisoxazoline ligands is indicated by stripes in the case of **3** ($n=3$, left). The conformation in the left is also presented by **3** ($n=1$, 2) and by **4**.

We know now that the enantioselectivity is determined by both the bisoxazoline and triflate chiralities and also that the chirality changes are brought about by just adjusting the geometry at the bridgehead carbon atom through variations in the size of the spirocyclic substituent in **3**. But, interestingly enough, the molecular chirality measures seem to be practically unaffected by the spirocyclic group itself, which is absent in fragment g. How then are the geometry changes at C^b transmitted to the rest of the molecule? The best clue we have found is a short distance between one of the two non-coordinated oxygens in each triflate arm and the α asymmetric carbon atom (Figure 7) in the corresponding oxazoline ring (approximately a constant distance of 1.81 Å, see Table 1), indicating a weak O···H-C hydrogen bond.[21] But the position of this hydrogen atom above and below the plane of the chelate ring varies with β, the C-C^b-C bond angle at the bridgehead carbon atom (Figure 8), which is in turn nicely correlated with the angle γ (Figure 1) at the cycloalkane ring, determined solely by the size of the cycloalkane ring. In the case of **3** ($n=4$), only one of the triflate groups is forming such a short contact, and this may explain why this compound has a different conformation of one of the triflate arms and, consequently, is significantly less chiral than the rest of the family. So it is reasonable to conclude that changes at the spirocyclic alkane are transmitted to the monodentate ligands through weak interactions with the H atoms at the asymmetric carbons of the oxazoline groups.

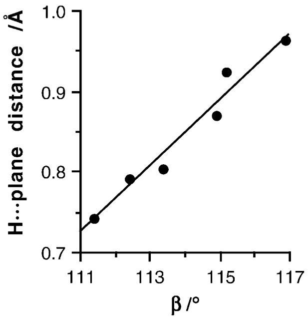


Figure 8. Relationship between the shortest distance of an α-H atom to the CuN_2 plane and the C-C_b-C bridgehead bond angle within the chelate ring **1**.

As a consequence of the correlation between the chirality measures S_f and S_g, the *ee* is also well correlated with the latter (Figure 9). It thus seems clear that the strain of the cycloalkane ring, represented by the bond angle γ, is transmitted to the chelate ring by modifying the bond angle at the bridgehead carbon atom, β, in a small but significant way. These bond angle variations modulate the spatial orientation of the side rings in **3**, thus modifying the voids through which the monodentate ligands may coordinate and decoordinate during a catalytic cycle.

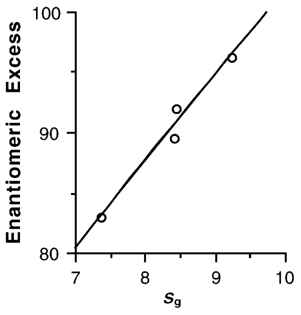


Figure 9. Enantiomeric excess of the complexes **3** as a function of the chirality measure of molecular fragment **g** (defined in Figure 4).

As our analysis has focused on **3**, one may wonder now whether a similar quantitative chirality analysis can apply to other families of bisoxazoline copper complexes, and particularly to active species that form during the catalytic cycle, in which the coordination positions occupied here by triflate ligands may be substituted by a dienophile. Dienophiles have been proposed to be coordinated through two carbonyl groups (as shown in **5**) in the catalytically active species,[22] and so the experimentally characterized structures of complexes **6** ($R^1 = t$Bu[23,24] or Ph[24]) may be suitable candidates. Since in these compounds the C_5 flaps and the pending oxygen atoms of the triflate ligands are missing, we cannot expect variations in the bridgehead bond angle β to affect the molecular chirality in the same way as in the family of compounds **3**. Indeed, the only correlation we have found between β and fragment chirality measures for these experimental structures (even if only three points are available) is with S_2, the chirality measures of the second coordination shell (atoms directly linked to the donor atoms) as seen in Figure 10. We stress that the *t*Bu derivative **6a**, with a negligible S_2 value, is deemed to be an inefficient enantiocatalyst, whereas the Ph derivatives **6b** have S_2 values of around 1.0 (see Figure 10) and have been experimentally found to be efficient enantioselective catalysts for the cycloaddition reaction between the related acrylimide and cyclopentadiene (**7**).[25] These results suggest that molecular chirality in the family of compounds **6** is mostly associated to that of the

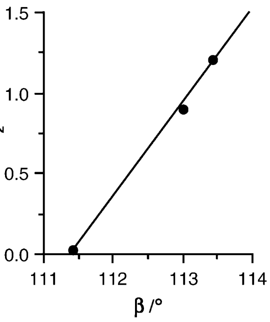
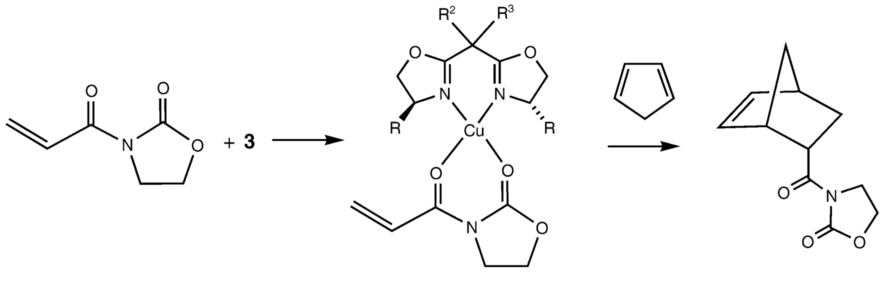


Figure 10. Chirality measure of the second shell in the copper(II) bisoxazoline complexes **6** as a function of the bridgehead bond angle within the chelate ring.



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metal coordination sphere, at difference with the family of complexes **3**, in which it depends to a significant degree also on the geometry of the bisoxazoline ligand. However, in both cases the bond angle β within the chelate ring seems to be a good parameter to calibrate molecular chirality.

In conclusion, we have seen that the relevant chirality of catalytic precursor **3** is associated with the orientation of the C_5 flaps at the bisoxazoline ligands which is twisted by the spiro-cycloalkane bridge. The C_5 flaps, in turn, affect the orientation of the monodentate ligands through weak hydrogen bonding and these contribute to molecular chirality as well. Following the quantitative chirality correlations presented here, it is predicted that **4** might give high *ee* in Diels–Alder reactions.

Programs Availability

Readers who would like to test and use our programs are encouraged to contact us at david@chem.ch.huji.ac.il

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