Enhancement of Enantiomeric Excess by Ligand Distortion

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Many advances have been made in the area of catalytic asymmetric induction and those developments have been highlighted in numerous reviews (since 1995 there have been in excess of 100 reviews written annually on the topic) culminating in the state of the art compendium *Comprehensive Asymmetric Catalysis* published in 1999.[1] These summarizing publications indicate that we are far from achieving the goals desired for chiral catalysts; while some catalysts perform well, most do not, even after extensive "tweaking".

In this communication we pose the following questions: (1) What relationship exists between the "chirality content" of a series of catalysts and their ability to carry out a stereodifferentiating task (in this case to induce asymmetry during a chemical reaction). Stated another way we ask: Do more chiral catalysts provide higher enantiomeric excesses (ee) than do less chiral catalysts for a given reaction? (2) Can one distort an existing chiral ligand in such a way as to make the catalyst even more chiral, and consequently, to increase the ee? This latter question is especially important because if the answer is affirmative, one can envision a number of ways to ply a ligand's substructure, e.g., by tethering parts together or by using buttressing groups and/or electrostatic effects to distort the ligand in a way that would enhance the stereoinduction. The answer to this second question is also important because one may be decreasing a ligand's capacity to induce asymmetry by, say, coordinating it to a metal with too small or too large a bite angle or some other distortion that may unwittingly result in lower ee than otherwise possible. Knowing the answers to these questions and defining which distortion modes may or may not impact a ligand's ability to perform optimally is an important aspect of catalyst design that has yet to be addressed. Here we show that (1) a linear relationship between chirality content and experimental ee exists for a homologous series of catalysts performing a cycloaddition reaction and (2) ligand distortions do lead to changes of chirality content, which, accordingly, will influence stereoinduction.

The catalysts we focus on are the Cu^{2+} coordinated spirocyclic bisoxazolines **1**−**4** first prepared by Davies et al. to assess the influence of ligand bite angle on the enantioselectivity of the Diels−Alder reaction between acrylimide **5** with cyclopentadiene to form, as the major diastereomer, the endo product **6**.[2] We select this system to study because it represents a typical bisoxazoline-based catalyst that is nowadays receiving a lot of attention,[3] but more importantly because a correlation between ligand bite angle and ee has already been noted (for a related study see Denmark and Stiff[4]).

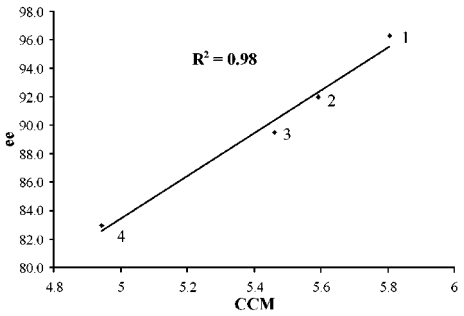
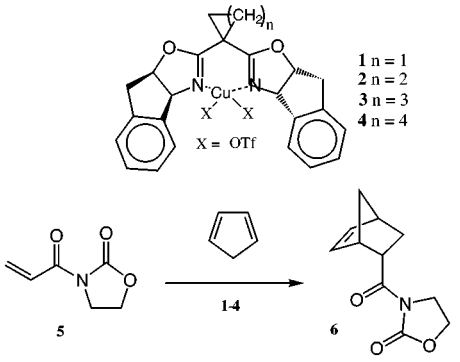


Figure 1. Plot of the computed chirality content (CCM) for catalysts **1**−**4** versus experimental enantiomeric excess of a cycloaddition. The structures used for the CCM calculation correspond to the lowest energy conformation of the spirocycle.



Although bite angle effects in metal-catalyzed C−C bond formation have been heavily studied and are well documented,[5] in the case of chirality, relying upon a single internal degree of freedom to make correlations with stereoselectivity is inappropriate because a catalyst's *chirality is a property of the whole molecule*. Accordingly, we need a *global chirality measure* for the task at hand and we have opted to use Avnir's Continuous Chirality Measure (CCM)[6−8] to compute the chirality content of the bisoxazoline catalysts. The CCM is calculated using eq 1,

$$S(\mathrm{G}) = \frac{1}{nD^2}\sum_{i=1}^{n}(p_i - \hat{p}_i)^2 \qquad (1)$$

where n are the number of vertexes located at positions p_i and given by symmetry point group G and the $\hat{p}_i$ are the corresponding points in the nearest G-symmetric configuration while D is a distance normalization factor to make the CCM value size-invariant. The CCM is a special distance function in that there is no ideal reference structure used for comparison a priori; rather, it is the distance to the nearest structure with the desired symmetry. In Figure 1 is a plot of computed catalyst chirality content versus experimental stereoinduction. A positive, smooth

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999.

(2) (a) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Chem. Commun.* **1996**, 1753−1754. (b) Davies, I. W.; Deeth, R. J.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1999**, *40*, 1233−1236.

(3) For leading references see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(4) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878.

(5) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769 and references therein.

(6) Zabrodsky, H.; Avnir, D. *J. Am. Chem. Soc.* **1995**, *117* (1), 462.

(7) The ability of the CCM approach to quantify structure−activity correlations in bioreceptors has been published: Keinan, S.; Avnir, D. *J. Am. Chem. Soc.* **1998**, *120* (24), 6152.

(8) Geometries used for the CCM calculations were derived using the PM3(tm) Hamiltonian in Spartan version 4.1, Wavefunction Inc.:, 18401 Von Karman, Suite 370, Irvine, CA 92715, USA. Conformational searches of the flexible spirocyclic groups were carried out with a stochastic-based method. All CCM values correspond to the lowest energy structures found for each catalyst. Ligand distortions were obtained by defining a coordinate and driving that coordinate in 1° increments for bite angle and 2° increments for pucker and twisting modes beginning from the global minimum of each catalyst.

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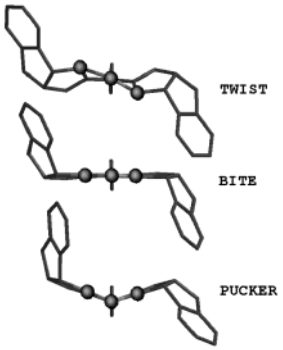

Figure 2. Distortion modes considered in this study. The reader is looking down the 2-fold axis of symmetry of molecule **1**; the copper atom is proximal to the reader and the spirocyclic carbon is distal. The X-ray and geometry optimized structures of these catalysts have a nearly planar N−Cu−N−C−C−C six-membered ring. The three spheres are the two nitrogen atoms coordinating with the Cu. All hydrogen atoms are removed for clarity.

correlation of apparent linearity between catalyst's chirality content and stereoinduction exists indicating that as CCM increases, so does the enantiomeric excess.

Having established that ee scales linearly with CCM we now address the second question posed above: Are there molecular distortions that can increase the CCM, and hence the ee? We have studied three types of distortions depicted in Figure 2: (1) changing bite angle, Φ, as defined in Davies' paper,[2] (2) puckering, and (3) twisting. We select these motions to assess what type of change will lead to an increase (or decrease) in chirality content. It is noted that only the puckering (butterfly) motion is symmetric in these catalysts; a 20° positive pucker is degenerate with a 20° negative pucker. Contrarily, a *P* twist differs from an *M* twist in these chiral systems (in one sense the aryl rings move toward one another, in the other sense they move apart), and a decrease in bite angle is not the same as an increase.[2]

Our results are presented in Figure 3. We begin our discussion with the influence of changing bite angle (top panel) where negative numbers refer to decreasing the bite angle and positive numbers indicate an increase in bite angle (from the equilibrium value). We find almost no change in chirality content as the bite angle is changed for structures **2** and **3**, but there are changes for **1** and **4**. The genesis of the discontinuity in CCM for catalyst **1** is that the system no longer remains planar after a 6° angle decrease; instead, it adopts a pucker that increases the chirality content. For catalyst **4**, decreasing the bite angle results in a continuous change in conformation of the cyclohexyl moiety that in turn increases the CCM value. Hence the increases in CCM for bite angle deformations originate from a pucker induced by the strained spirocyclopropyl group or from a conformational change in the spirocyclohexyl ring. Otherwise we find the chirality content to be insensitive to change in bite angle.

In the middle panel of Figure 3 are plotted the CCM values for the butterfly motions. For this distortion mode there are smooth increases in chirality content as the system is puckered (the small bumps for catalyst **4** originate from small structural changes in the flexible cyclohexyl moiety). Hence one concludes that by puckering these systems one increases the chirality content, and because chirality content scales linearly with ee, the ee will increase with pucker.

In the bottom panel of Figure 3 we present plots of CCM as a function of twisting. In these plots, contrary to those above where the minimum CCM values are at the equilibrium molecular structure, we find that CCM values increase for the negative twisting direction (the one moving the centriods of the aryl rings apart) while twisting in the other direction decreases the CCM from that of the catalyst's equilibrium geometry. Also noted in

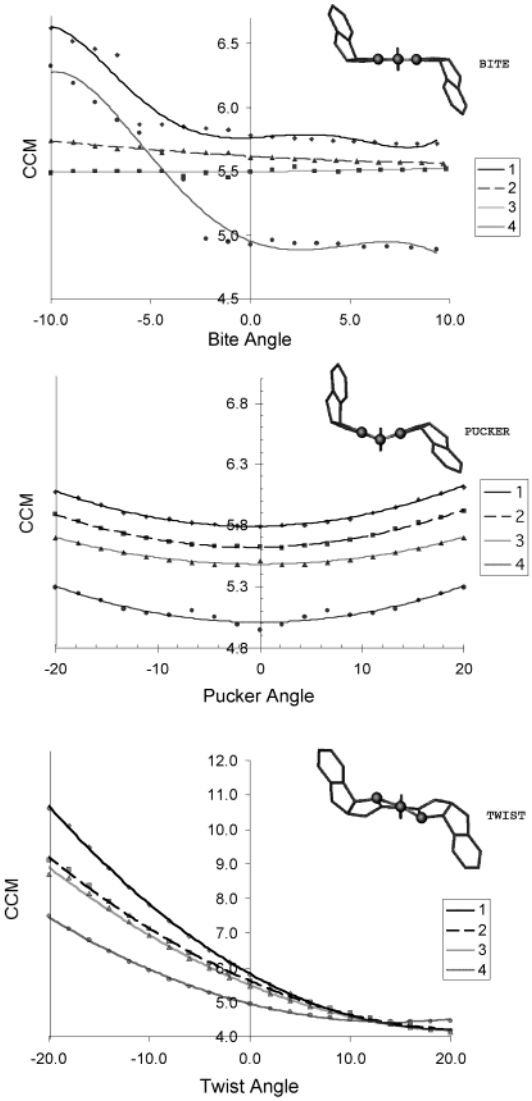

Figure 3. Chirality content as a function of molecular distortion.

these plots is the finding that changes in chirality content are much larger in magnitude for twisting motions than for puckering (almost no changes take place for purely planar bite angle changes). The maximum amount of twist we envisage one could accommodate in such systems is −15° based on computed strain energies. Hence, if one wished to pursue a strategy of increasing ee by distorting a bisoxazoline substructure, it is this distortion mode to focus on.

To summarize, we have demonstrated that the CCM, a global measure of molecular chirality content, scales apparently linearly with stereoinduction for a series of catalysts performing the same task. Moreover, we have demonstrated that deforming these catalysts can lead to changes in CCM which then must influence experimental ee. For metal-coordinated bisoxazolines we find the influence of ligand distortion to be twist > pucker > bite. The results presented here describe, for the first time, that ligand distortions do affect stereochemical outcome and that one must pay attention to this issue because one may, unwittingly, be decreasing ee's that a ligand might otherwise provide.

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