Enantiofacially Selective Binding of Prochiral Olefins to a Chiral Catalyst via Simultaneous Face−Face and Edge−Face Aromatic Interactions

Roger W. Quan, Zhen Li, and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology
Harvard University, Cambridge, Massachusetts 02138

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Small-molecule chiral catalysts are capable of effecting reactions with enzyme-like enantioselectivity, without sacrificing the substrate generality associated with simple synthetic reagents. Synthetic catalysts and enzymes both exert stereoinduction through molecular recognition events, yet the former are usually analyzed in terms of steric *destabilization* of the pathway leading to the minor enantiomeric product, while the latter are thought to operate by transition state *stabilization* in the pathway leading to the major enantiomer.[1] In reality, the basis for selectivity in reactions of these catalysts may not be so different, as several examples of effective synthetic chiral catalysts have been uncovered wherein attractive, noncovalent secondary interactions between substrate and catalyst are suggested or strongly indicated by experiment.[2] The incorporation of enzyme-like recognition elements into simple catalysts is clearly an appealing design feature, since attractive interactions can, in principle, reduce conformational degrees of freedom and enhance chiral discrimination in selectivity-determining transition states.[3]

We recently discovered that C_2-symmetric 1,2-diimines are effective ligands for Cu(I)-catalyzed enantioselective aziridination and cyclopropanation reactions.[4] Closely related Cu(II) complexes of the same ligands have also been applied to the catalysis of highly enantioselective Diels−Alder reactions.[5] These diimine ligands thus establish highly differentiated asymmetric environments for copper-mediated reactions of alkenes, a phenomenon that is somewhat surprising given their simplicity and apparent high degree of conformational flexibility. During the course of our studies on these catalyst systems, we successfully crystallized complex **1** bound to styrene and characterized its solid-state structure (Figure 1).[6] This structure has unanticipated characteristics which may hold broader implications for the design of ligands for asymmetric catalysis.

The X-ray crystal structure reveals a complex with a distorted trigonal planar copper center bearing a chelating diimine ligand and a π-bound styrene. The PF_6^- counterion is noncoordinating. The distances between Cu and the vinylic carbons C1 and C2 (Figure 1) are 1.98 and 2.05 Å, consistent with other crystallographically characterized Cu(I)−olefin complexes.[7] Most significant, the C_2-symmetric diimine ligand is arranged such

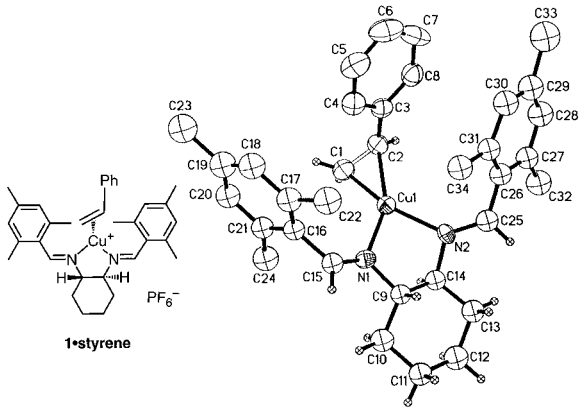

Figure 1. Line drawing and thermal ellipsoid plot (50% probability level) of the X-ray crystal structure of **1·styrene**.

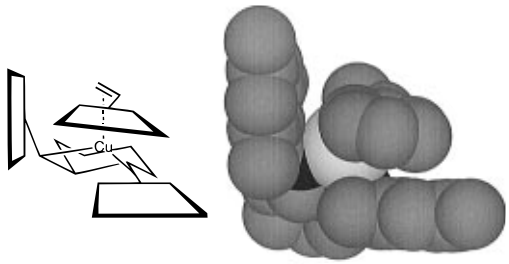

Figure 2. Space-filling representation of the X-ray crystal structure of **1·styrene** highlighting the orthogonal disposition of the ligand aromatic groups.

that its two aromatic groups are almost perfectly orthogonal to each other, with the aromatic group of the styrene lying squarely in the resulting cleft (Figure 2). No intermolecular contacts are apparent in the structure.

Substantial experimental[8] and theoretical[9] effort has been directed toward characterizing noncovalent interactions between aromatic groups in well-defined systems. The distance between the centroids of aromatic groups in documented edge-to-face complexes falls in the range of 4.5−7 Å,[10] with a theoretically predicted[9a] optimal distance of 5 Å; in the **1·styrene** complex, this distance is 5.2 Å. In addition to one of the aromatic ortho hydrogens, the *cis*-β-hydrogen on styrene also enjoys an apparent bonding interaction with the centroid of the ligand aromatic group (Figure 3A). The separation between the aromatic planes in the face-to-face interaction of **1·styrene** is 3.26 Å (Figure 3B), again in line with the measured distance in reported structures ($\leq$3.6 Å).[11]

Simultaneous face−face and edge−face aromatic interactions between substrate and chiral ligand have been proposed to play a critical role in defining the enantioselectivity in the Sharpless asymmetric dihydroxylation reaction.[2c] The high levels of chiral recognition obtained with the commercially available and widely useful Whelk-O HPLC columns have also been analyzed in the

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(2) (a) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (c) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470. (d) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319.

(3) For a review of π-stacking effects in asymmetric synthesis, see: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.

(4) (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

(5) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027.

(6) The **1·styrene** complex was prepared by treating $[Cu(CH_3CN)_4]PF_6$ with 1 equiv of the corresponding diimine ligand[4b] in dichloromethane followed by the addition of 10 equiv of styrene. Solvent removal at 0 °C, followed by recrystallization from dichloromethane, afforded X-ray quality crystals.

(7) (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889. (b) Thompson, J. S.; Whitney, J. F. *Inorg. Chem.* **1984**, *23*, 2813. (c) Matsuda, H.; Machida, K. *J. Chem. Soc., Dalton Trans.* **1988**, 1907.

(8) For recent reviews, see: (a) T. Dahl *Acta Chem. Scand.* **1994**, *48*, 95. (b) Nishio, M.; Umezawa, Y.; Hirota, M; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665. See also: (c) Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561. (d) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497. (e) Cozzi, F.; Cinquini, M.; Annuziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729.

(9) (a) Jorgensen, W. L.; Severance, D. L. J. *J. Am. Chem. Soc.* **1990**, *112*, 4768. (b) Groves, J. R.; Walters, E. A.; Hui, E. T. *J. Phys. Chem.* **1987**, *91*, 3233.

(10) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. Blundell, T.; Singh, J.; Thornton, J.; Burley, S. K.; Petsko, G. A. *Science* **1986**, *234*, 1005.

(11) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.

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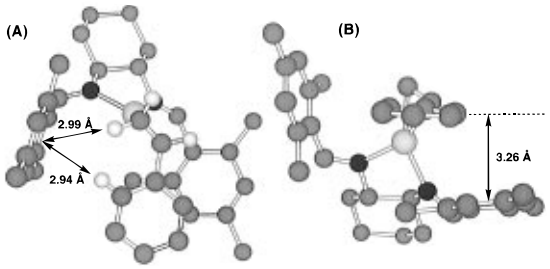


Figure 3. (A) Edge−face aromatic interactions (B) face−face aromatic interactions in the solid-state structure of **1·styrene**.

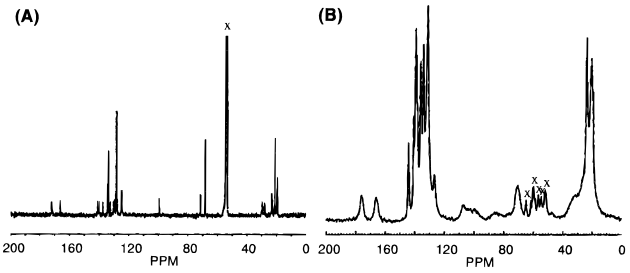


Figure 4. ^{13}C NMR spectra of **1·styrene** complex: (A) Solution spectrum (CD_2Cl_2) at −90 °C (peak marked with × is due to solvent); (B) CPMAS spectrum taken at a spinning rate of 3.99 kHz (peaks marked with × are spinning sidebands).

context of such attractive aromatic interactions.[12] However, to our knowledge, the structure of **1·styrene** constitutes the first example of a crystallographically characterized chiral complex displaying both types simultaneously and intramolecularly with a chiral or prochiral guest.[13]

The relevance of the X-ray crystal structure of **1·styrene** to the structure of the complex in solution was assessed in a series of NMR experiments. The room temperature ^{13}C NMR spectrum (CD_2Cl_2) exhibits the expected resonances for a C_2-symmetrical complex,[14] consistent with rapidly reversible olefin complexation on the NMR time scale. At −90 °C, this equilibration is slowed, as evidenced by resonances corresponding to a complex with C_1 symmetry (Figure 4A). Preferential binding of one enantioface of the alkene to the chiral complex is evident upon inspection of the imine carbon region, which displays only two equivalent resonances (δ 166 and 172) corresponding to the diastereotopic imine carbons. The ^{13}C CPMAS spectrum[15] (Figure 4B) corresponds almost perfectly with the the solution spectrum at −90 °C, indicating that the edge-to-face and face-to-face aromatic interactions evident in the X-ray crystal structure are also present in solution.

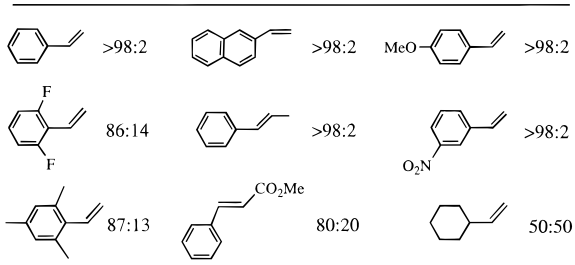
(12) Pirkle, W. H.; Liu, Y. *J. Org. Chem.* **1994**, *59*, 6911.

(13) For examples of crystallographically characterized model systems displaying these interactions, see: (a) Harmata, M.; Barnes, C. L. *J. Am. Chem. Soc.* **1990**, *112*, 5655. (b) Harmata, M.; Barnes, C. L.; Karra, S. R.; Elahmad, S. *J. Am. Chem. Soc.* **1994**, *116*, 8392. A 1:1 complex exhibiting both face-to-face and edge-to-face interactions within an infinite network has also been described: Ishida, T.; Tarui, M.; In, Y.; Ogiyama, M.; Doi, M.; Inoue, M. *FEBS Lett.* **1993**, *33*, 214.

(14) This spectrum is included as supporting information. The NMR samples were prepared by treating 1 equiv of the diimine ligand in methylene chloride-d_2 with 0.5 equiv of $[Cu(OTf)]_2 \cdot C_6H_6$ followed by 1.5 equiv of the alkene.

(15) Solid-state ^{13}C spectra were obtained on a Bruker MSL200 NMR spectrometer. Results from cross polarization magic angle spinning experiments carried out at 3.99 and 2.5 kHz were used to interpret the spectral data.

Table 1. Enantiofacial Selectivity of Complexation of Selected Olefins to **1** As Determined by ^1H NMR at −90 °C (CD_2Cl_2)



Low-temperature ^1H NMR spectra of **1·styrene** also provide strong evidence for exclusive binding of one styrene enantioface to the chiral copper complex, with a single set of diastereotopic imine proton resonances present at −90 °C. The importance of the secondary aromatic−aromatic interactions to the enantioselectivity of complexation was evidenced by analysis of the ^1H NMR spectrum of **1** in the presence of 2,6-difluorostyrene. With this substrate, two sets of diastereotopic proton resonances were present in an 86:14 ratio.[14] The reversal in polarization of the C−F bond relative to the C−H bond at the ortho aromatic positions of this substrate results in the loss of available edge−face interactions with the ligand aromatic groups, and this is the apparent source of diminished enantiofacial selectivity in the complexation.

This NMR method for evaluating the enantiofacial selectivity of olefin complexation was extended to a series of other alkenes (Table 1). Enantiofacial selectivity in binding of 2,4,6-trimethylstyrene to **1** (87:13) was almost identical to that of 2,6-difluorostyrene, reinforcing the notion that edge−face interactions with the chiral ligand are precluded for both substrates. Interestingly, the presence of electron-donating or electron-withdrawing substituents on the styrene derivative (e.g. *p*-methoxystyrene and *m*-nitrostyrene) had no detrimental effect on binding selectivity. Aliphatically substituted alkenes such as vinylcyclohexane were found to bind with no measurable selectivity.

The solution and solid-state structures of alkene complexes of **1** thus provide strong evidence that attractive edge−face and face−face aromatic interactions can play a determining role in enantioface discrimination in binding of prochiral substrates to this class of chiral catalysts. Such secondary catalyst−substrate interactions may also play an important role in catalysis, and we are currently exploring the design and application of chiral complexes which incorporate this design principle.

Acknowledgment. We thank Dr. Joseph Ziller at the University of California, Irvine for solving the crystal structure and Dr. Robert Lee at the California Institute of Technology for assistance in obtaining the ^{13}C CPMAS spectral data. This work was supported by the National Science Foundation (PYI program) and by the David and Lucille Packard Foundation through awards to E.N.J.

Supporting Information Available: Crystal data and details of the structure refinement for **1·styrene**; tables of atomic coordinates, bond lengths and angles, anisotropic displacement parameters, and structure factors. The ^{13}C NMR spectrum of **1·styrene** obtained at 23 °C and the imine resonances from the −90 °C ^1H NMR spectra of **1·styrene** and **1·2,6-difluorostyrene** (12 pages). See any current masthead page for ordering and Internet access instructions.

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