That **9a**, **9b**, and **9c** belong to the same series was proven by partial hydrogenation of **9a** (Wilkinson's catalyst, toluene)[13] to **9b** (58% yield next to starting material), and by comparison of the relevant ^{1}H NMR spectral data of **9b** and **9c** which were identical except for the low-field resonance at $\delta = 3.03$ of H20 (absent in **9c**) and the doublet at $\delta = 0.93$ of the protons at C21 (singlet in **9c**). The final unambiguous identification of the structures in the **9**-series was established by the X-ray diffraction analysis of crystalline **9c**.[14]

Although full understanding of the process will necessitate further experiments to minimize the apolar fraction, the described cyclization of **8** is remarkable in that it constitutes a rare example of a nonenzymatic polycyclization that leads to anti-Markovnikov like cyclization products with a six-membered C-ring (**9**, **10** and **12**). The reactions are furthermore characterized by bond formation at vicinal quaternary centers.[15, 16] The "natural" pathway, which is now believed to involve a classical Markovnikov cyclization to a five-membered C-ring followed by ring expansion,[9] is considered in our case to be less likely,[12] although this alternative cannot be excluded at this stage.[17] The observed 20*R* configuration further confirms what one may have expected on the basis of chemical intuition: 1) the chain folding in the D-region is one that minimizes the steric interaction between C20 and the methyl group at C14, and 2) the C17 to C20 hydride shift which establishes the absolute configuration at C20 occurs faster than rotation at the C17–C20 bond. The analogy between structures **5b**/**6b** and **9b**/**10b**, respectively, is also striking. It may indicate that the cyclohexane ring at the 11,12 bond operates as a mimic of a rather tight binding of the central part of the natural substrate in the hydrophobic cleft of the enzyme.[18]

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[13] Relevant procedures and spectroscopic data are given as Supporting Information.
[14] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-140162 (**9c**) and -140169 (**12a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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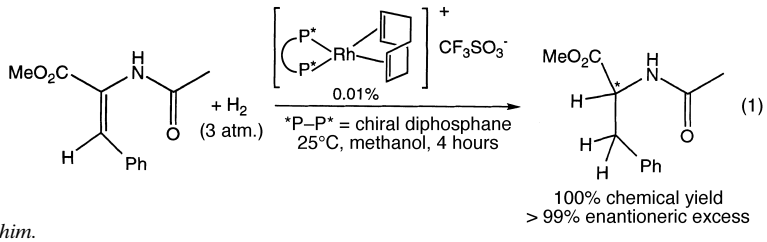
A Simple Model for the Origin of Enantioselection and the Anti "Lock-and-Key" Motif in Asymmetric Hydrogenation of Enamides as Catalyzed by Chiral Diphosphine Complexes of Rh(I)**

Clark R. Landis* and Steven Feldgus

The historical and commercial significance of catalytic, enantiospecific enamide hydrogenation[1–4] has generated intense interest in the reaction mechanism [Eq. (1)].



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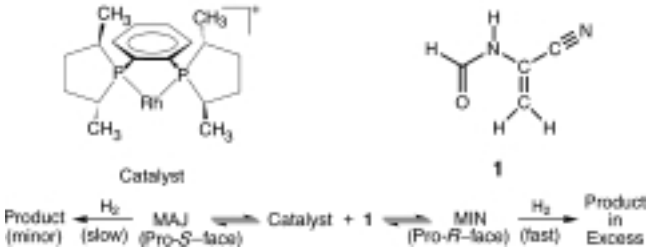
Investigations led by Halpern and Brown elucidated a surprising anti "lock-and-key" mechanistic motif, in which the major product enantiomer arises from hydrogenation of the C=C enantioface that binds less favorably to the catalyst.[5–8] Why these catalysts exhibit such anti "lock-and-key" behavior and how widely this mode of stereochemical control applies to other catalysts are unanswered questions. We present results of computer modeling studies, which suggest a simple model for enantiospecificity in enamide hydrogenation and, in the process, demonstrate the power of modern computational methods in catalysis research.

The kinetic studies of Landis and Halpern established the following mechanism for the catalytic hydrogenation of enamides: Reversible binding of the substrate to the catalyst followed by rate-determining activation of H_2 and the subsequent rapid elimination of the hydrogenated product.[8] For a chiral catalyst and a prochiral enamide, the catalytic cycle consists of two diastereomeric manifolds, designated Major (MAJ) and Minor (MIN), in correspondence with the relative stabilities of the Rh-substrate adducts.[8] The product, which can be produced in an enantiomeric excess (*ee*) as high as 99.9 %, is generated almost exclusively by the small fraction (< 10 %) of the catalyst in the minor diastereomeric manifold.

We have computed free-energy surfaces for the hydrogenation reaction of a model enamide, α-formamidoacrylonitrile (**1**), as catalyzed by the highly selective, chiral catalyst, $[Rh\{(R,R)\text{-Me-DuPHOS}\}]^+$ (Me-DuPHOS = 2′,5′,2″,5″-tetramethyl 1,2-bis(phospholanyl)benzene; Scheme 1).[9, 10] As in a previous investigation of the achiral catalyst, $[Rh(PH_3)_2]^+$,[11] we chose the amidoacrylonitrile, rather than the more common amidoacrylate species,[12] because hydrogenation of acetamidocinnamonitrile has been shown to yield a high *ee*, comparable to methyl acetamidocinnamate, and because nitrile groups span a smaller conformational space.[2] We present results of gas-phase three-layer hybrid ONIOM computations.[13] The enantiospecificities of enamide hydrogenations are commonly insensitive to the nature of the solvent, which justifies a gas-phase analysis.[14]



Scheme 1. Catalyzed hydrogenation of **1**.

The computed properties of the diastereomeric catalyst–substrate adducts, pro-*S* MAJ and pro-*R* MIN, agree with experiment (Figure 1).[8, 15–17] The enamide substrate binds to the (*R*,*R*)-Me-DuPHOS-ligated catalyst in a bidentate fashion, with coordination of both the amide oxygen and the C=C double bond. Metal binding to the substrate's pro-*S* face (MAJ) is stabilized with a free energy of 3.6 kcal mol^{-1} at 298 K relative to the pro-*R* face (MIN), which corresponds to a 500:1 ratio of [MAJ]:[MIN].

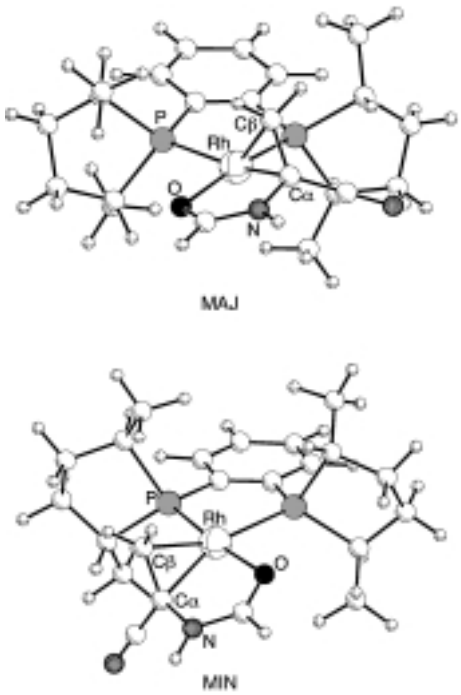
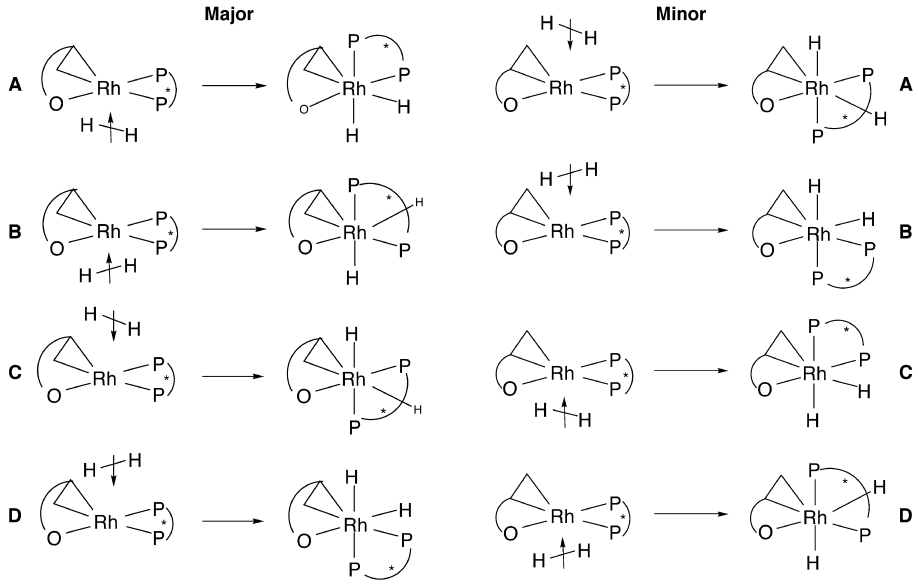


Figure 1. Computed structures of the catalyst–substrate diastereomers.

In principle, reaction of MAJ and MIN with H_2 leads to eight diastereomeric reaction pathways, as illustrated in Scheme 2.[5, 18] We have followed all eight pathways computa-



Scheme 2. Eight possible pathways arising from *cis* addition of H_2, either along the C-Rh-P axis (**A** and **C**) or along the O-Rh-P axis (**B** and **D**).

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tionally. Each pathway proceeds along the same sequence of elementary steps: First, an ion-induced dipole complex (IID) of hydrogen and the catalyst–enamide cation is formed. Addition of H_2 yields a five-coordinate, trigonal bipyramidal molecular H_2 complex ($MOLH_2$). Oxidative addition of H_2 generates the six-coordinate dihydride intermediate (DIHY). Migratory insertion of C=C into the Rh–H bond forms the alkyl hydride intermediate (ALHY). Finally, reductive elimination generates the hydrogenation product, still coordinated to the catalyst. Direct experimental evidence for the intermediacy of alkyl hydride complexes has previously been published[19] and the overall sequence of elementary steps agrees with previous proposals.[8, 20] As we previously found for the achiral model system, $[Rh(PH_3)_2(\mathbf{1})]^+$,[11] only the **A** pathways are kinetically active. The free energy surfaces for these pathways are shown in Figure 2. Significant participation of the **B**, **C**, and **D** pathways is precluded by $>20\,kcal\,mol^{-1}$ barriers in at least one of the elementary steps; the origins of these barriers are electronic as they are found both in the simple model system and the sterically bulky DuPHOS system.

Taking into account the initial difference in stability of MAJ and MIN, we find the free energy of activation for the minor diastereomer to be $4.4\,kcal\,mol^{-1}$ lower than the major diastereomer. Thus, the anti "lock-and-key" motif, in which the less stable diastereomer produces the most product, is reproduced by computation.[21]

Why is MAJ more stable than MIN? The primary difference between the two structures, as seen in Figure 1, is that the α-carbon lies closest to the coordination plane for MAJ; for MIN, the β-carbon lies in the coordination plane. We approximate a $7\,kcal\,mol^{-1}$ energetic penalty for placing the β-carbon, rather than α-carbon, in the coordination plane as follows: Mutation of the DuPHOS methyl groups of MAJ and MIN into H atoms followed by geometric optimization of only the phospholane rings creates sterically relaxed diastereomers with the α-carbon and β-carbon, respectively, in the coordination plane. The structure derived from MIN is $7\,kcal\,mol^{-1}$ higher in energy than that derived from MAJ. Subsequent optimization of the full structures produces a pair of energetically identical enantiomers with the α-carbon lying in the coordination plane. For the fully methylated DuPHOS, steric interaction between a DuPHOS methyl group and the substrate β-methylene forces the α-carbon out of the coordination plane and destabilizes MIN relative to MAJ.

Why is MAJ so much less reactive toward H_2 than MIN? Quadrant maps[1] qualitatively illustrate the primary steric interactions that occur when H_2 adds to either diastereomer (Figure 3). Addition of H_2 to MAJ is disfavored by motion of the nitrile group across a hindered quadrant. This motion yields both a high energy molecular hydrogen intermediate and a high energy transition state for formation of the dihydride. In contrast, the sterically induced distortion of MIN, which results in the β-carbon of the alkene lying in the coordination plane, *promotes* reaction with H_2. Adoption of the trigonal bipyramidal structure of the molecular hydrogen complex is unencumbered as the nitrile group swings across an unhindered quadrant and requires little net motion. After the molecular hydrogen complex is formed, both manifolds have similar barriers for the subsequent steps (oxidative addition, migratory insertion, and reductive elimination).

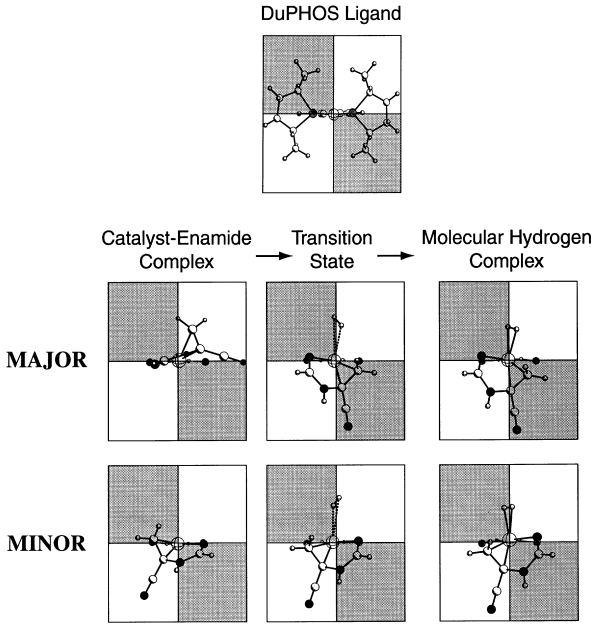

Figure 3. Formation of the molecular hydrogen complexes as viewed from a quadrant diagram perspective. For both pathways, hydrogen adds parallel to the P-Rh-C axis from the side of the β-carbon.

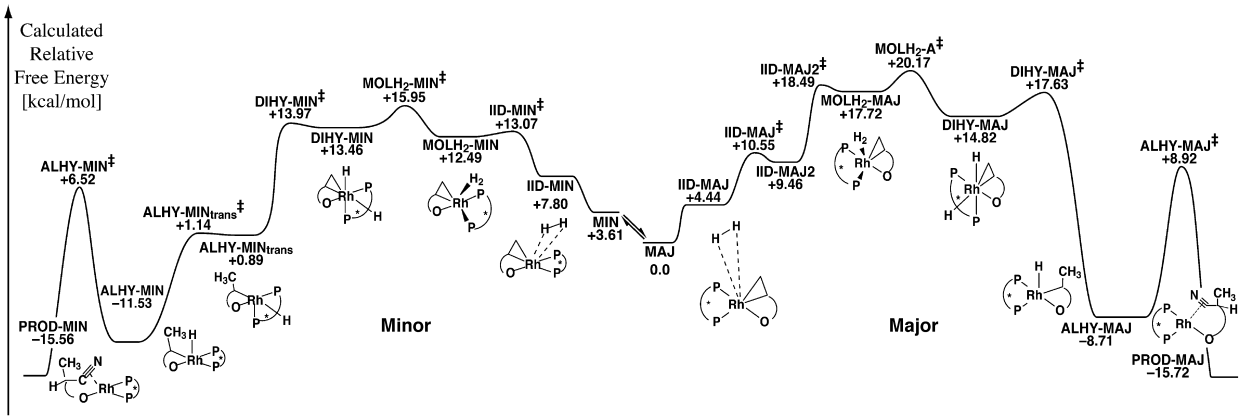

Figure 2. Free energy diagrams for pathway **A** on both diastereomeric manifolds at 298 K. Energies are in $kcal\,mol^{-1}$ and are referenced to the energy of MAJ.

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The computational results agree well with all relevant empirical results. Computation predicts the following. 1) A 99.8% *ee* at 298 K in favor of the *R* product for hydrogenation of enamides with the [Rh{(*R*,*R*)-Me-DuPHOS}]$^+$ catalyst, similar to the >99% *ee* of *R* products routinely observed experimentally for closely related substrates.[9, 22] 2) The equilibrium concentration of MIN should be less than 0.25%, in accord with the failure of NMR experiments to detect the MIN diastereomer of [Rh{(*S*,*S*)-DuPHOS}-(enamide)]$^+$ adducts.[23] 3) Dihydrides are intermediates in the catalytic cycle[24] although not at levels detectable by common NMR methods due to their high free energies and the low barriers for migratory insertion. Recently, Bargon and co-workers have reported direct observation of dihydrides by the very sensitive *para*-hydrogen induced polarization (PHIP) method during the hydrogenation of dimethyl itaconate.[25] 4) Similar activation free energies for H_2 activation and reductive elimination steps. Previous studies involving different diphosphines[19] have shown that lowering the temperature can result in a switch from rate-determining H_2 activation to rate-determining reductive elimination.

It is intriguing that enantiospecificities of enamide hydrogenation are quite sensitive to the nature of the enamide α-substituent.[26] We anticipate that modulation of the electronic characteristics of the α-substituent will significantly affect both the orientation of the enamide to the coordination plane in the square planar catalyst–substrate adducts and the relative stabilities of the α- and β-alkyl hydrides. Computational evaluations of such effects are in progress.

Computational Methods

The three ONIOM[13] layers (B3LYP:HF:UFF) are defined as follows: The core layer (B3LYP) consists of the enamide, H_2, rhodium, and an ethylene bridged bis-phosphine ligand (hydrogen atoms replace the phospholane rings); the intermediate layer (HF) includes the core plus the phospholane rings without the methyl groups; and the outer layer (MM) consists of the entire molecule (B3LYP = Becke's 3-parameter hybrid functional with Lee, Yang, and Parr correlation energies; HF = Hartree–Fock; MM = Universal Force Field molecular mechanics). All intermediates and transition states were fully optimized at the ONIOM (B3LYP/LANL2DZ:HF/LANL2MB:UFF) level of theory in a modified version of Gaussian 98[27] (these modifications can be found in the Supporting Information). Intermediates were verified by the absence of negative frequencies and transition states were verified both by the presence of a single negative eigenvalue and by optimization in both directions along the negative eigenvector coordinate. All structures reported in this paper were fully reoptimized using ONIOM (B3LYP/II:HF/LANL2MB:UFF), where II refers to an expanded (311111/22111/411) basis set for rhodium[28] and a 31/31 basis set for phosphorus.[29] An additional d function with an exponent of 0.34[30] was added to the P atoms. All other atoms used a 6-31G(d,p) basis set. Free energies were taken unscaled from the thermochemical section of the vibrational frequency analysis. No attempt was made to correct for hindered rotation vibrational entropy.

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