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Prediction of Enantioselectivity in Rhodium Catalyzed Hydrogenations

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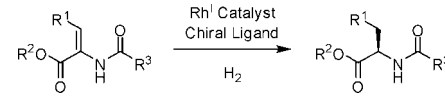
Enantioselective synthesis of chiral compounds has grown into one of the most heavily investigated areas of organic chemistry.[1] One important reaction in this area is the enantioselective hydrogenation of enamides for the synthesis of natural or unnatural α-amino acids (Scheme 1).[2] In this reaction, the choice of a chiral ligand for the metal catalyst is critical.[3] Trial-and-error and high throughput screening can be expensive both in cost of materials and in time.[4] Increasing the success rate by virtual screening would therefore be highly desirable.

Computational screens in asymmetric catalysis can be based on QSAR-like approaches,[5] and a simple quadrant model of this type has in fact been applied to the title reaction.[6] An alternative is direct modeling of diastereomeric transition states,[7] which for large, flexible systems is only feasible by force field-based methods.[8] The QM-guided molecular mechanics method (Q2MM)[9] yields a transition state force field which offers a high potential accuracy at the price of a substantial investment in parameter development. We previously developed Q2MM parameters for the title reaction.[10] Here, we demonstrate the successful, rapid *in silico* screening of chiral catalysts for the hydrogenation of enamides as the first application of this model.

The ligand set shown in Figure 1 consisting of BINAP derivatives (**A**−**E**),[11] PHANEPHOS (**F**),[12] DIPAMP (**G**),[13] 1,2-bis(phospholano)cyclopentanes (**H**,**I**),[14] and alkyl P-chiral (**J**−**M**)[15] ligands was chosen to provide a structural diversity of ligands that does not overlap with the training set used in the development of the model[10] and was obtained under similar reaction conditions while also providing a wide range of experimentally observed enantioselectivities. The substrates chosen all generate alanine (**1**, **2**) or phenylalanine derivatives (**3**−**7**) with a variety of protecting groups to provide real-world test cases. The use of various substrate derivatives highlights the usefulness of the method to screen not only potential chiral ligands but also protecting groups that may play a significant role in affecting the stereochemistry of the product. A comparison of computed and experimental[11] values for the hydrogenation of substrates **1**−**3** using the BINAP ligands **A**−**E**, giving a range of ee's, from 99% to 14.8%, is shown at the top of Figure 2. The overall agreement is very good with a mean unsigned error of 0.8 kcal/mol, demonstrating the fast and reliable identification of promising and unpromising ligands.

The maximum energy error of 1.5 kcal/mol occurred for ligand−substrate combination **E1**, where the observed ee of 92.3% was overestimated with a >99% calculated. Conversely, the largest error in ee was observed with the three substrates hydrogenated with the unfunctionalized BINAP ligand **A**, which all exhibited poor ee's with errors ranging from 4.3% to 42.7%. The virtual screening would be considered successful in that **A** would be eliminated from the library for experimental screening as the low ee's correspond to very small energy differences, ranging from 0.1 to 0.5 kcal/mol.

Scheme 1. Rh-Catalyzed Hydrogenation of Enamides



Next, we investigated a typical problem for the practical application of the reaction, the question of which ligand and/or protecting group should be used for a given substrate. Five phenylalanine derivatives **3**−**7** and eight structurally diverse ligands **F**−**M** giving experimentally observed enantioselectivities of 23.0% to 99.9% ee were studied.[12−15] All starting materials generate phenylalanine derivatives. Substrates **3** and **5** with ligand **G** were evaluated in both the *Z* and *E* geometries, whereas all others were exclusively *Z* substrates. The reactions were performed between 20 and 50 °C, under a hydrogen atmosphere ranging from 1 to 5 atm, and performed in methanol as the solvent.[12−15] None of these varying reaction conditions were included as variables in the screening process. The theoretical predictions and comparison to experimental values are shown at the bottom of Figure 2. The agreement between theory and experiment is very good and again reliably identifies promising candidates for experimental confirmation. Similar to the results discussed earlier, the mean unsigned energetic error is 0.8 kcal/mol, while the maximum absolute error 2.5 kcal/mol was slightly higher than that obtained for the BINAP ligands. The potential and accuracy of the methods are best demonstrated by the fact that although the method was originally designed as a semiquantitative screening tool, quantitative agreement between theory and experiment is found for over 90% of the cases studied. The linear regression analysis for the experimental and predicted ee's for the 29 data points reported here gives an R^2 value of 0.92 (see Supporting Information, SI).

The deviation is almost entirely due to three data points (**B3**, **E3**, and **G3E**) which suggests a specific physical reason for the deviations between theory and experiment. All involve substrate **3** for which ligands **B**, **E**, and **G** gave false positive results with predicted ee's of 80.6%, 93.1%, and 77.0% but experimental values of 23.2%, 44.8%, and 23% for **B3**, **E3**, and **G3E**, respectively. These three ligands are some of the most sterically demanding in the data set studied here. The large BINAP ligands **B** and **E**, combined with a large substrate, generate a sterically crowded complex wherein the addition of hydrogen is hindered in both diastereomeric complexes. This crowding suggests that the reaction can take place only when the ligand or substrate is partially dissociated. Such a mechanistic change, which has recently been studied in detail for bulky ligands,[16] is of course not modeled correctly by the reaction-specific force field.[10] The hypothesis that a mechanistic change takes place is further supported by the finding that the computed low-energy structures of **B3** and the sterically

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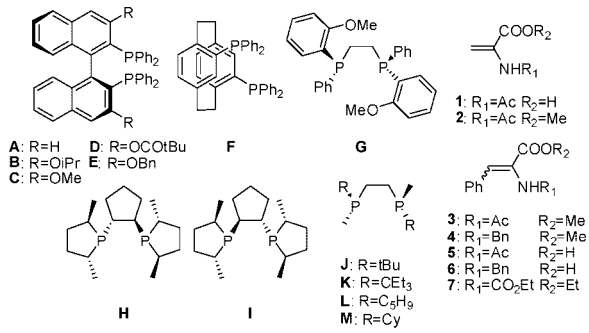

Figure 1. Ligands (**A**−**M**) and substrates (**1**−**7**) used in test set. Substrates **3**−**7** are in the *Z* orientation unless otherwise specified.

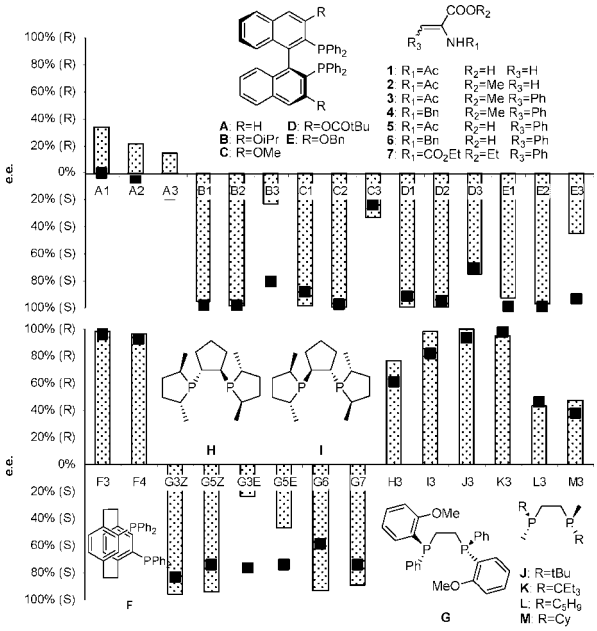

Figure 2. Comparison of theoretical (■) and experimental (bars) ee's using ligands **A**−**E** (top) and **F**−**M** (bottom).

less congested **B1** are very similar and give similar predictions for the ee but experimentally give very different ee's.

A survey of the available experimental data also supports this hypothesis. It is known that **G3Z** and **G5Z** give ee's of 96% and 94%, respectively, whereas the *E*-enamide variants gave lower ee's of 23% for **G3E** and 47% for **G5E** and react almost 100 times more slowly than the *Z*-isomers.[17] The structural origin of these experimental findings can be explored using the calculated structures. The orientation of the substrate moiety in the transition structure orients the group in the *Z* position of the enamide away from the chiral ligand, while in the *E* position it is directed toward the ligand. This distorts the phenyl rings of the ligand away from the substrate, which alters this conformation from the lowest energy conformation that they adopt when the *Z*-enamide is used. This destabilizing interaction in the transition state could lower the rate for reaction of the *E*-isomer and favor other mechanistic pathways. A mechanistic change may involve a partial dissociation of the substrate or the ligand to relieve the steric strain, leading to a change in the observed enantioselectivity.[16] Cartesian coordinates for the lowest energy structures of **B3**, **E3**, **G3E**, and **G3Z** are available in the SI.

In summary, the Q2MM method requires substantial development times for each reaction type under study but, in return for this investment, yields a fast tool with high accuracy. The excellent performance ($R^2 > 0.90$) of the virtual screening of a ligand library for the enantioselective catalytic hydrogenation of enamides suggests that similar reaction-specific force fields can be derived for many other enantioselective reactions. Future applications of the strategy to other industrially important reactions as well as much larger virtual libraries will explore the generality of this approach, which has the potential to fundamentally change the process of ligand selection from a trial-and-error driven process to the combination of virtual screening and experimental confirmation that is used extensively in drug discovery. Finally, the possibility of rapidly predicting the enantioselectivity of related reactions not only permits ligand selection but also adds significant value to the wealth of available information for organometallic reaction mechanisms. As such, it could provide a novel mechanistic tool through the quantitative rather than more common qualitative use of stereochemistry as a mechanistic probe.

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Supporting Information Available: Computational details, selected Cartesian coordinates, and detailed statistical analysis of the calculated data points. This material is available free of charge via the Internet at http://pubs.acs.org.

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