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Using Physical Organic Parameters To Correlate Asymmetric Catalyst Performance

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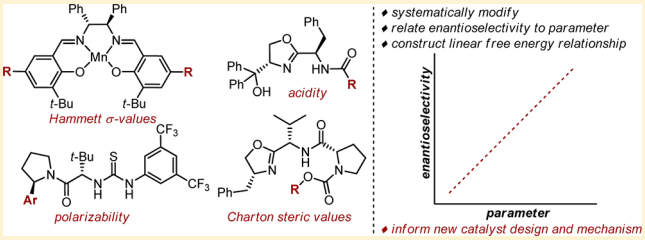
ABSTRACT: A classic strategy of physical organic chemists is to probe reaction mechanisms using linear free energy relationships. Identifying such relationships in asymmetric catalytic reactions provides substantial insight into the key factors controlling enantioselectivity, which in turn increases the predictability and applicability of these reactions. The focus of this JOCSynopsis is to highlight several recent examples in which various parameters were identified and applied to the elucidation of LFERs.



INTRODUCTION

The modern intersection of physical organic chemistry and asymmetric catalysis has enabled the elucidation of the interactions responsible for asymmetric induction while providing a platform for improving catalyst performance and informing new catalyst design. In this regard, the identification and application of linear free energy relationships (LFERs), which correlate substituent effects of a catalyst or substrate to resultant enantioselectivity, has been a key contributor. LFERs were developed as a powerful tool in physical organic chemistry relating a well-defined reference reaction rate ($\Delta\Delta G^{\ddagger}$) or equilibrium constant ($\Delta\Delta G^{0}$) to reactions of interest. Correlations between said reference data and a reaction under investigation allows key mechanistic inferences to be established. Application of LFERs in asymmetric catalysis holds great potential as the mechanism of asymmetric induction is difficult to examine through other techniques largely because of the finite energy differences of diastereomeric transition states leading to enantiomeric products. Specifically, LFERs afford a potential predictive capability and illuminate the influence of a substituent to ultimately edify improvements to catalyst performance. The purpose of this JOCSynopsis is to discuss the types of parameters used to develop LFERs and other related correlations in asymmetric catalytic reactions.

CURTIN–HAMMETT PRINCIPLE

The fundamental basis for constructing correlations between catalyst properties and enantioselectivity is the relationship $\Delta\Delta G^{\ddagger} = -RT\ln(k_{rel})$ where k_{rel} is the relative rate of formation of one enantiomer over the other. This enantiomeric ratio can be easily measured by chiral separation chromatography.[1] In order to apply correlative analysis to enantioselective catalysis, the Curtin–Hammett principle must be considered.

A simple interpretation of the Curtin–Hammett principle dictates that in reactions where there are multiple interconverting intermediates leading to a distribution of products, the distribution is principally determined by the difference in free energy between diastereomeric transition states, not the equilibrium energies of intermediates (Figure 1).[2−4] In terms

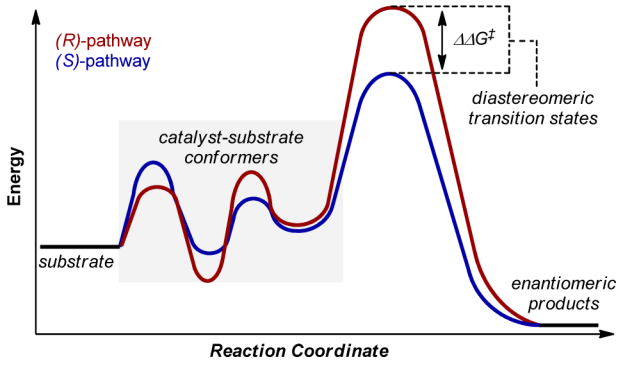


Figure 1. Generic catalytic asymmetric reaction coordinate that demonstrates the key features of the Curtin–Hammett principle.

of asymmetric catalysis, this principle is applicable to catalyst–substrate interactions through the step that determines enantioselectivity. A simple illustrative example is a substrate binding to a chiral catalyst, which likely involves diverse interactions and geometries. Assuming the binding is reversible and barrier(s) to interconversion is low relative to the enantiodetermining step, the enantiomeric ratio (er) observed should be attributed solely to $\Delta\Delta G^{\ddagger}$ and not the populated conformational states. As described by Halpern, the catalyst–substrate interactions are assumed to be much weaker than the bond formation or cleavage events, indicating that the Curtin–Hammett principle can be applied, if cautiously, in asymmetric catalysis.[4,5]

$\Delta\Delta G^{\ddagger}$ is only a curiosity in the context of a single measured enantioselectivity, but examining $\Delta\Delta G^{\ddagger}$ as a function of a series of systematically perturbed reaction parameters provides a

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glimpse into key features affecting the transition state free energies. The assumption in observing correlations using a series of catalysts or substrates is that the energies associated with the transition states are perturbed without affecting the mechanism of asymmetric induction. If a correlation is observed, it implies that the mechanism of asymmetric induction is robust to changes in the system, an important observation in its own right.

A key aspect in developing correlations is identifying appropriate catalyst elements that can be systematically modified and parametrized. In this regard, a modular catalyst is ideal to increase the ability to synthetically access probe molecules. These changes need to be accurately parametrized in order to encapsulate the properties of interest.[6] Below we outline specific case studies by parameter selection.

Hammett Electronic Parameters. The seminal report of a LFER in asymmetric catalysis was described by Jacobsen and co-workers in the context of the Mn(salen)-catalyzed asymmetric epoxidations of *cis*-alkenes.[7] This reaction was uniquely qualified for LFER analysis as the salen ligand template is synthesized in a modular manner (Figure 2).[8]

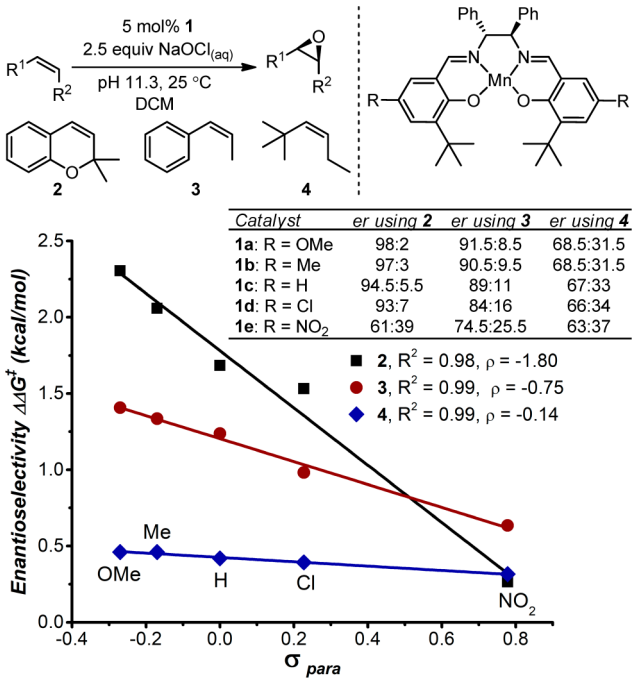

Figure 2. Hammett correlations of enantioselective epoxidation using substituted Salens.

Catalyst assessment revealed a correlation between ligand electronic variation and enantioselectivity.[9] To quantify this electronic effect, Hammett σ-parameters, derived from the acidities of substituted benzoic acid, were used.[10−17]

cis-2,2-Dimethylchromene, *cis*-β-methylstyrene, and *cis*-2,2-dimethyl-3-hexene were all separately evaluated, and each revealed a LFER with catalyst electronic (Figure 2). The same general trend was observed for each substrate with electron-donating salens yielding the highest enantioselectivity. The sensitivities toward the catalyst electronic nature varied by substrate with *cis*-2,2-dimethylchromene displaying the greatest sensitivity.

To explain these observations, Jacobsen and co-workers invoked the Hammond postulate and hypothesized that the nature of the electronic effect was through bias for a more product-like transition state. Specifically, a negative ρ-value is observed indicating that electron-donating ligands lead to higher enantioselectivity. This suggests the formation of a more stabilized Mn(V)-oxo species, effectively making it a weaker oxidant and decreasing the rate of epoxidation. The weaker oxidant requires greater proximity of the alkene substrate and a later transition state, which implies enhanced substrate/catalyst interactions leading to higher enantioselectivity. These hypotheses were further substantiated through kinetic isotope effects, Eyring analysis, and computational studies, all of which indicated that a more product-like transition state was reflected by the electronic effect.[18]

Also supporting this hypothesis was a more recent study reported by Pericás and co-workers in which they examined the role of substrate electronics under modified epoxidation conditions using the commercial Jacobsen catalyst **5**.[19] They found a strong correlation between substrate electronics and enantioselectivity using trisubstituted olefins (Figure 3).

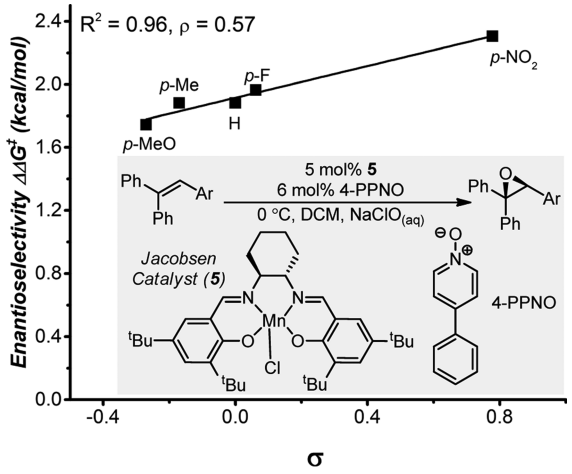

Figure 3. Plot of enantioselectivity as a function of substrate electronics.

Electron-rich alkenes, which are more reactive toward oxidation by the Mn(V)−oxo species, gave lower enantioselectivities, while electron-poor alkenes, requiring a later transition state, gave higher enantioselectivities. Comparison of the ρ-values between the catalyst and substrate LFER reveals that the reaction is less sensitive to substrate electronics although the substrates evaluated by Pericás and co-workers are of conjugated alkenes, wherein electronic effects are likely mitigated.

Brønsted Acidity. Jensen and Sigman probed a variant of the enantioselective hetero-Diels−Alder (HDA) reaction first reported by Rawal and co-workers.[20−24] They were interested in the reaction in order to showcase a modular catalyst scaffold designed to be capable of H-bond catalysis; camphorsulfonamide-derived catalyst **6** was initially found to be optimal (Figure 4).[25,26] Initially, it was assumed that the high enantioselectivity observed using **6** was due to the bulky nature of the camphor appendage. Therefore, the authors were surprised to discover a pronounced effect on enantioselectivity by investigation of simplified amides.[27] Catalyst series **7a−e** revealed that more acidic catalysts yielded higher enantioselectivities for the HDA reaction. To develop the LFER, the pK_a's of the corresponding acetic acids as measured in H_2O

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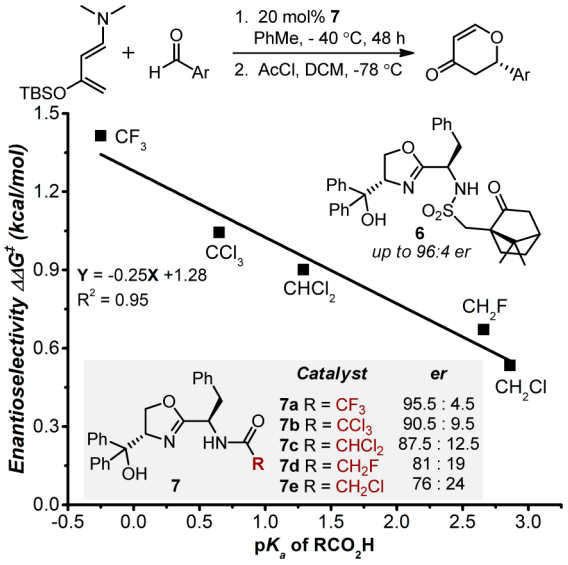

Figure 4. Correlation of enantioselectivity as a function of catalyst acidity for the HDA reaction.

were employed as a measure of Brønsted acidity.[1,28] While inherent differences in H-bonding and traditional Brønsted acid catalysis need to be considered, the observed correlation implicates the strength of the H-bond formed between the substrate carbonyl and the catalyst N−H bond is directly impacting enantioselectivity.

To explore the effect of amide N−H bond acidity on the system, a kinetic study was undertaken.[29] The rate-determining step was shown to be the cycloaddition and not catalyst binding of the substrate. Kinetic data also suggested that the acidity of the catalyst affects the rate of substrate binding as well as the rate of reaction with the diene.

To further examine the system, the authors exploited another modular aspect of the system, namely the aldehyde substrate. In contrast to catalyst effects, evaluation of a series of 4-substituted aldehydes yielded no sensitivity between their electronic nature and the enantioselectivity of the reaction. However, a Hammett correlation between substrate electronics and rate was observed at both low and high aldehyde concentrations, which is consistent with rate-determining cycloaddition. At first glance, the strong correlation between catalyst acidity and enantioselectivity and the lack of correlation between substrate electronics and enantioselectivity is confusing. If stronger H-bonding occurs as a result of effectively pairing pK_a's of the donor and acceptor, a relationship between substrate electronics and enantioselectivity would be expected.[30,31] Another hypothesis was formulated that explains the lack of substrate electronic effects via application of the Hammond postulate.[32] Specifically, higher catalyst acidity stabilizes the buildup of negative charge on the carbonyl oxygen during the transition state, which more closely resembles a product-like benzyl alcohol. The electronic substituent effects of benzyl alcohols have much less variation than the corresponding benzoic acids. The range of pK_a's of *para*-substituted benzyl alcohols is ∼0.6 pK_a units, whereas the pK_a range of the substituted benzoic acids is ∼3.2.

Polarizability. Hydrogen bonding is a common motif for transition-state stabilization in enzymes. Another common motif is cation−π interactions,[33−35] which refer to the stabilization of cationic intermediates via electrostatic interaction with a π-system, typically an arene. This stabilization is facilitated by the polarizability, or the ability to disseminate charge, of a molecule. Inspired by reports of these cation−π interactions in nature, Jacobsen and Knowles designed a catalyst capable of highly enantioselective polyene cyclizations.[36,37] The catalyst combined the anion-binding capabilities of thioureas as well as an arene moiety capable of stabilizing a cation via a cation-π interaction. The model reaction they studied was the bicyclization of hydroxyl lactams, which are known to ionize under acidic conditions (Figure 5).

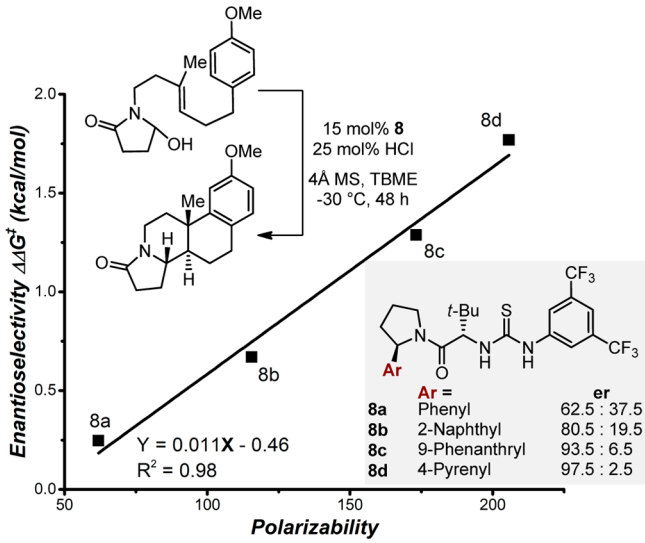

Figure 5. Plot of enantioselectivity as a function of arene polarizability in the asymmetric bicyclization of hydroxyl lactams (see refs 40 and 41 for details of this parameter).

The catalyst designed made use of the well-characterized bistrifluoromethylphenyl thiourea employed by many in this field,[38] connected by an amide linker to a chiral aryl pyrrolidine. Proof of their concept was exhibited by catalyst **8a** in the model system, although with low enantioselectivity (Figure 5). Expanding the surface area of the aryl ring led to vastly improved enantioselectivities. It should be noted that the reaction forms three new contiguous stereocenters through separate bond-forming events, and the reported enantioselectivities are for the single diastereomer formed in the reaction.

To determine the role of the arene, Jacobsen and Knowles correlated enantioselectivity with arene polarizability for catalysts **8a−d** (Figure 5).[39] Although this is not formally a LFER (a LFER relates two free energies as suggested by its definition), the correlation is compelling as it relates $\Delta\Delta G^{\ddagger}$ (enantioselectivity) to a physical organic parameter. The measure of an arene's polarizability is its capability of delocalizing charge through distortion.[40,41] The correlation between polarizability and enantioselectivity implies that the catalysts stabilize the cationic intermediates by delocalizing positive charge.[42,43] Extrapolation of this correlation indicates aryl rings with greater polarizability would generate higher enantioselectivity, although this has not yet been reported.

The aforementioned correlation implicates the ability of the extended π-systems to stabilize cationic charge but did not rule out that the aryl ring's effect is steric rather than electronic in nature.[36,37] To delineate the role of the arene, they evaluated the effect of temperature on enantioselectivity with each catalyst. The resultant Eyring analysis showed that varying the

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aryl ring had a primarily enthalpic effect. This is consistent with energetic stabilization of the cationic intermediates, as such stabilization would be primarily enthalpic with a negligible entropic element.[44] Conversely, if the role of the aryl ring was primarily a steric effect, the Eyring analysis would have revealed an entropic effect relating to substrate ordering. This correlation between catalyst polarizability and enantioselectivity not only constitutes a unique relationship but also quantifies an important design element in asymmetric catalysis.

Charton Steric Parameters. Steric effects are arguably the most widely implicated design controlling factors in asymmetric catalysis. Although several sets of experimentally based steric parameters have existed for years, until recently there was no significant effort to correlate steric effects to enantioselectivity.[45−54] Sigman and co-workers became interested in the Nozaki−Hiyama−Kishi (NHK)-type additions to carbonyls as a platform for a similar amino acid−oxazoline ligand template as described above.[55,56] Through initial empirical studies, a significant steric effect was revealed when manipulating the ligand carbamoyl group. This observation, in combination with the modular nature of the ligand template, provided the impetus for further investigation into the role of the carbamate. A model system was selected using catalyst framework **10** to examine both the allylation of benzaldehyde and acetophenone (Figure 6).[45] Variation of the carbamoyl group gave a series of

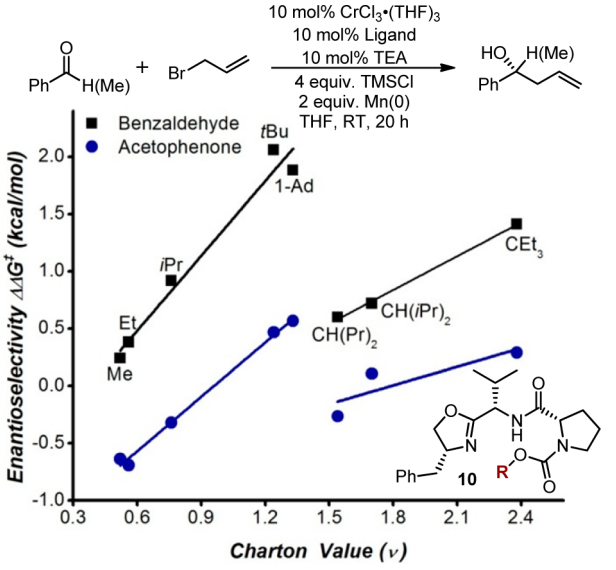

Figure 6. Plot of the enantioselectivity of the NHK allylation as a function of Charton steric parameters showing the nonlinear nature for larger substituents.

ligands **10a−e**, which were evaluated in the model reactions. The results showed significant sensitivity to the presumed steric effects at this position. The steric effects were quantified by applying Taft-based Charton steric parameters.[57−59]

Applying Charton's parameters to the NHK allylation reaction led to a strong correlation between the substituent's size and the enantioselectivity (Figure 8). The slopes also indicated that the reaction was very sensitive to substitution at the carbamate position. Using the available Charton parameters, three larger substituents were selected for incorporation into the ligand and subsequent evaluation in the NHK reaction. Using the LFER, the enantioselectivities for these substituents was predicted to be beyond the previously reported optimized system. However, evaluation of these catalysts manifested a break in the correlation and rendered the LFER ineffective as a predictive tool.[60]

Evaluation of other reported data revealed that Charton steric parameters could correlate steric effects in numerous systems.[60] In contrast to the previously discussed LFERs, this LFER was used as a design element more than a tool to derive the mechanism of asymmetric induction. This study also represents the first successful attempt to correlate steric effects in asymmetric catalysis and reveals Charton parameters as a potential tool to examine such effects. The break in correlation was identified as a point of further study and has since been explained as a potential misapplication of the Charton parameter.[45,53]

Computed H-Bond Length. Among organocatalytic reactions, few have received as much attention as the enantioselective Strecker reaction.[61] Jacobsen and co-workers have had a long interest in developing a highly enantioselective Strecker reaction with the culmination, after more than a decade of work, recently reported by Jacobsen and Zuend.[62−65] In an effort to understand the subtleties of this powerful reaction, they undertook a physical organic, and computational study of their system.[66]

As a part of their kinetic and optimization studies, they generated a small library of thiourea based catalysts (Figure 7).

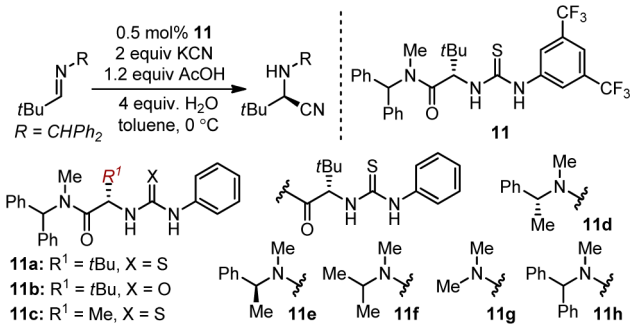

Figure 7. Library of catalysts used to evaluate the Strecker reaction.

Upon first inspection, these catalysts possess different properties and do not contain a complementary set of variations, as would be required to develop a traditional LFER. Using this set of catalysts, they computed the energy differences between the major and minor enantiomeric pathways at three different levels of theory, B3LYP/6-31G(d), M05-2X/6-31+G(d,p), and MP2/6-31G(d). In each case, correlation was found between the calculated $\Delta\Delta E^{\ddagger}$ and the observed $\Delta\Delta G^{\ddagger}$. Interestingly, B3LYP/6-31G(d) was shown to be the most accurate level of theory for the system, despite its propensity to underestimate the energies associated with noncovalent attractive interactions.[67−69] Although the calculations consistently overestimate the $\Delta\Delta E^{\ddagger}$ values, the correlation to observed enantioselectivity suggests that the error is systematic. Also, the computation correctly predicted the growing energetic preference for the (*R*)-enantiomer across the catalyst set. Considering the amount of variation within the catalyst library, the correlation verifies the viability of computation for examining the system.

Exploring the computed structure for each catalyst revealed no obvious steric interaction that could explain increased enantioselectivity. The spatial arrangement of atoms was either static through the series or deemed inconsequential to the enantioselective outcome. This observation raised the question

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of how the variation in enantioselectivity is achieved for the different catalysts. In fact, the calculations revealed no significant difference in the H-bond lengths between the (*R*) or (*S*) product-forming pathways for highly or poorly enantioselective catalysts. However, their computational work had revealed that the computed rate-determining step of the reaction was rearrangement of the ion pair through a carbonyl stabilized H-bonding network (Figure 8). They examined the

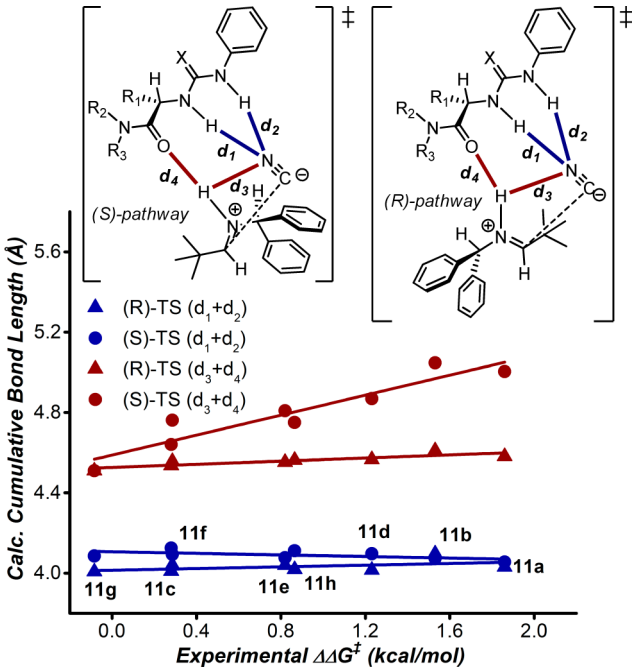

Figure 8. Calculation of the proposed enantiodetermining transition states leading to the (*R*)- and (*S*)-enantiomers (B3LYP/6-31G(d)). The key bonding interactions are labeled and plotted as a function of experimentally observed enantioselectivity.

role of this H-bond network through this step and identified no robust correlation between the cumulative H-bond distances in the (*R*)-selective pathway. However, in the (*S*)-selective pathway, they observed a correlation between cumulative H-bond distance and enantioselectivity.

This correlation provides compelling evidence that the source of enantioselectivity is due to weaker stabilization of the imminium ion in the (*S*)-pathway. For the more enantioselective catalysts, the amide carbonyl becomes less accessible in the preferred transition state geometry inherent to the (*S*)-pathway, which leads to its destabilization relative to the (*R*)-pathway. This highlights another feature of H-bonding not discussed previously: the bonding orientation is impactful. In this system, there are no direct steric interactions that explain destabilization of a specific pathway. Instead, the steric effect arises from the catalyst itself, where its low energy conformation presumably leads to subtle differences in the amide carbonyl direction relative to the thiourea. This, in turn, leads to increased differences in the H-bonding network responsible for stabilization of the key intermediate.

CONCLUSION

The power of LFERs and related correlations is only now being realized in asymmetric catalysis. The ability to correlate enantioselectivity can lead to rational catalyst improvements, prediction of catalyst performance, and increased understanding of catalyst dynamics. All of this information is of great interest to those developing and applying asymmetric catalytic reactions.

Correlative techniques can be complementary to computation-based designs, and the combination of the two is a powerful approach where computation can be used to arrive at unique parameters and can itself be correlated to enantioselectivity. The merging of the two techniques appears to be mutually beneficial as computational techniques often require experimental validation and LFER analysis is limited by known experimental parametrizations.

To maximize the information inferred from the experimentally or computationally based parameters, particularly in regard to transition-state structure, various well-understood reactions must be studied through correlation to generate a comparative data set. The variety of parameters discussed might imply that the field is rich with examples of correlations but, regrettably, only a handful of other examples of correlations in asymmetric catalysis have been reported.[70−72] Given the information attainable through such application, the hope is that this number will grow in the coming years.

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Notes

The authors declare no competing financial interest.

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Kaid Harper recently completed his Ph.D. in Prof. Matthew Sigman's laboratory at the University of Utah and is currently a postdoctoral researcher in Prof. Eric Jacobsen's laboratory at Harvard University.

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Matthew Sigman joined the faculty of the University of Utah in 1999, where his research group has focused on the development and mechanistic studies of new synthetic methodology.

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