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Examination of the Role of Taft-Type Steric Parameters in Asymmetric Catalysis

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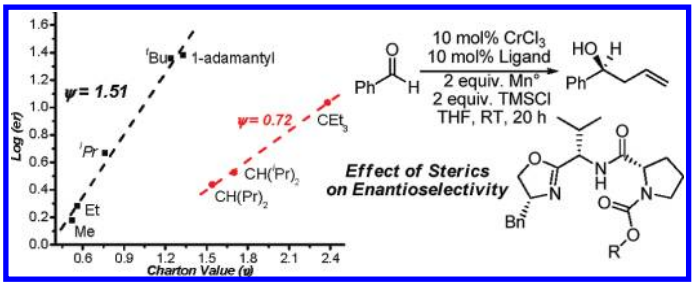

We report the use of Taft steric parameters to correlate the substituent size of a ligand with the enantiomeric ratio of a reaction. Linear free energy relationships can be constructed by plotting the log of enantiomeric ratio (er) versus the steric parameters reported by Taft and modified by Charton. Successful correlations were found for aldehyde and ketone allylation under NHK conditions using modular oxazoline ligands developed in our laboratory. Using these correlations, ligands were designed and evaluated for carbonyl allylation reactions. A break in the Charton plot results and is attributed to a global structural change in the catalyst. Additionally, several previously reported enantioselective reactions are analyzed resulting in excellent correlations for both catalysts and substrates. Finally, limitations and issues are presented with illustrative examples.

Introduction

In 1894, Emil Fischer proposed the "lock and key" model for substrate/enzyme interactions implicating the importance of the size of a substrate in relationship to the active site of an enzyme.[1] Although molecular interactions are clearly more complex than this model suggests, steric effects,[2] or the repulsive spatial interactions encountered within or between molecules, are commonly evoked in explaining observed reaction outcomes, as originally suggested by Ingold in 1930.[3] A steric hindrance explanation is generally qualitative in nature in contrast to the widely used quantitative methods for exploring electronic effects through linear free energy relationships (LFER).[4] Quantitative methods do exist for analysis of steric effects (vide infra)[5] but are not commonly employed in the analysis of a reaction mechanism, presumably due to the difficulty in interpreting the results or synthetically accessing the necessary analogs to perform the study.

An area of modern organic chemistry which often suggests a steric effect is asymmetric catalysis.[6] Chiral ligands utilized in enantioselective reactions are often designed to "hinder" an approach from a certain prochiral face of the substrate to enhance enantioselection. The incorporation of a larger substituent is often the first synthetic modification made to a promising ligand structure. Considering the potential of a lengthy synthetic endeavor to prepare and evaluate a designed ligand as well as the unanticipated outcomes often found in asymmetric catalysis, we became interested in correlating steric parameters to enantiomeric ratios for

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facilitating the design of new ligands.[7] Recent efforts in asymmetric catalysis design have focused on using computational methods to predict the outcome of enantioselective reactions and the design of improved catalysts.[8] However, for catalyst systems which have complicated/unidentified structures, these methods are difficult to implement. Our approach is based on a more classic evaluation of steric parameters using LFERs developed by Taft and Charton wherein the nature of the catalyst structure or assumptions related to reactive species are not initially necessary. It should be noted that Taft steric parameters have been used to correlate enantioselectivity as a function of substrate substituents as reported by Porter but not previously as a function of ligand substituents.[9,10] Herein, we describe the investigation of ligand and substrate effects in asymmetric catalysis using steric parameters developed by Taft[11] and Charton[12] with examples from ligands developed in our laboratory as well as illustrative examples from previously reported asymmetric catalytic processes. In addition, the limitations and potential applications are discussed.

Taft-Type Steric Parameters. The correlation of reaction rate to electronic parameters is a well-known and widely used method to probe the mechanism of chemical reactions. Among the most common methods are Hammett and Brønsted linear free energy relationships.[13] Correlations of this type are measurements of electronic effects and do not take into account steric parameters that might also contribute to the overall rate of the reaction in question. In fact, the rates of hydrolysis of many ortho-substituted benzoates do not fit Hammett analyses.[3] This is in contrast to the often excellent correlations of the corresponding para- and meta-substituted substrates.[14] The rates of hydrolysis of ortho-substituted benzoates decrease as the relative size of the ortho-substituents are increased, suggesting a steric effect. Seminal research by Taft sought to explore this possibility, ultimately allowing for the correlation of steric parameters to reaction rate.[11a]

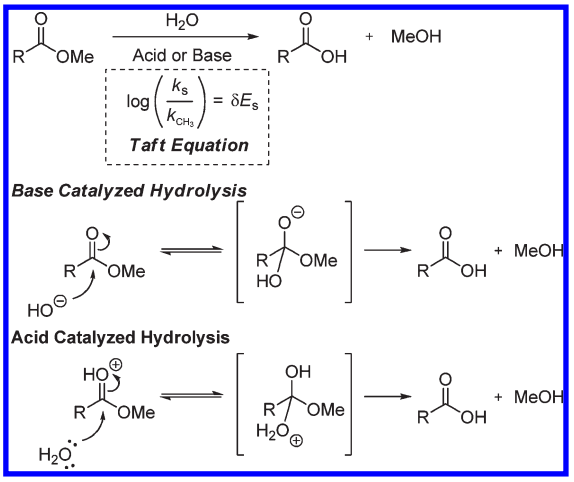

FIGURE 1. Taft's correlation of methyl ester substituents to the rate of hydrolysis in the development of Taft's steric parameters.

In the original studies, the relative rates of methyl ester hydrolysis were measured for a wide range of aliphatic esters (Figure 1).[11a,b] The equation shown in Figure 1 reflects the steric influence of substituents on the rate of hydrolysis, where k_s is the rate of ester hydrolysis for a given substrate, k_{CH_3} is the methyl acetate hydrolysis rate, which is used as the standard, δ is a proportionality constant which is a measure of sensitivity, similar to the ρ value in a Hammett plot, and E_s is defined as the Taft steric parameter, analogous to a σ value in a Hammett plot. The key hypothesis presented by Taft to isolate the steric impact on hydrolysis rate was based on the nature of the conditions employed. If hydrolysis is conducted under basic conditions, the reaction involves the conversion of a neutral reactant to a negatively charged intermediate. Therefore, Taft proposed the transition state would be influenced by polar effects (resonance and induction) and would be an inaccurate measure of steric influences.[8c] The acid-catalyzed pathway, however, involves a charged intermediate formed from a charged precursor and therefore should be influenced by polar effects to a much lesser degree. Additionally, the steric influence of the proton was assumed to be minimal. These assumptions result in a relationship between the size of the substituent and the rate of hydrolysis, $\log(k_s/k_{CH_3}) = \delta E_s$. This analysis has been applied to various organic and biological chemical processes[15] and has been used in medicinal chemistry via quantitative structure (re)activity relationships (QSAR).[16] The E_s values for several common substituents are tabulated in Table 1.

Following the development of Taft's method for steric correlation there was considerable debate in the 1960s and

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TABLE 1. Taft and Charton Steric Parameters for Common Substituents

substituent	$-E_s$ (Taft)	ν (Charton)
H	−1.24	0
Me	0	0.52
Et	0.07	0.56
^{n}Pr	0.36	0.68
^{n}Bu	0.39	0.68
^{i}Pr	0.47	0.76
^{c}C$_6$H$_{11}$	0.79	0.87
PhCH$_2$	0.38	0.7
^{t}Bu	1.54	1.24
1-adamantyl		1.33
Ph	2.54	0.57 and 1.66
CH(^{n}Pr)$_2$		1.54
CH(^{i}Pr)$_2$		1.70
CEt$_3$		2.38

1970s concerning E_s values and the notion that they were purely a measure of steric effects.[13d,17] In order to address this, Charton correlated the E_s values with the van der Waals radii of the corresponding group, ruling out both inductive and resonance effects.[12] The resultant equation is $\log(k/k_0) = \psi\nu$, where the log of the relative rate (k/k_0) is proportional to the product of ψ (sensitivity factor) and ν, and ν is the adjusted E_s value based on the van der Waals radii[18] of the given substituent. Some common substituents and their corresponding ν values are presented in Table 1.

Results and Discussion

Applying Taft-Based Steric Parameters to Asymmetric Catalysis. An ultimate goal of correlating steric parameters to the outcome of an enantioselective reaction is predicting what type of modification to the ligand structure would result in an optimized catalyst system with the least synthetic effort. To approach this, a modular ligand set derived from simple and readily available building blocks is optimal to allow for various modifications to be introduced. To this end, we have been interested in peptide-derived α-amino-oxazoline ligands which can be rapidly synthesized from amino acid building blocks.[19] These ligand sets have been successfully applied to the enantioselective allylation of aldehydes and ketones under Fürstner[20] modified Nozaki−Hiyama−Kishi (NHK) conditions in which allylic halides are the allyl source.[21] For both aldehyde[22] and ketone substrates,[23] excellent enantiomeric ratios (er) can be obtained for aromatic carbonyl derivatives but reactions with aliphatic carbonyl substrates lead to only modest er.

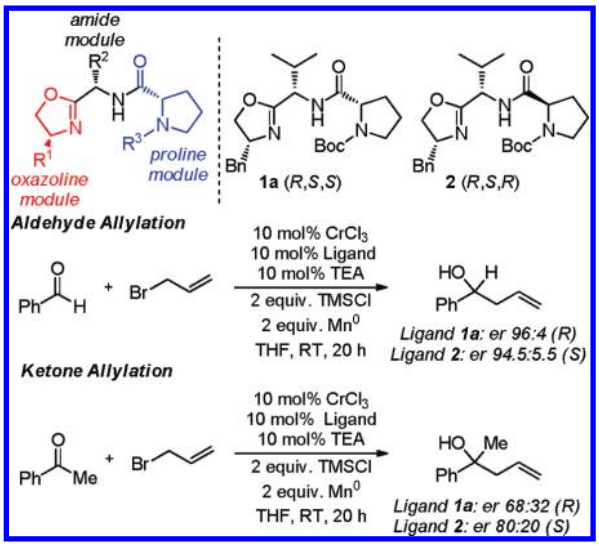

FIGURE 2. Effect of the proline module on facial selectivity in the Cr-catalyzed addition of allyl bromide to carbonyl compounds.

One intriguing observation in these studies is that the facial selectivity of aldehyde and ketone allylation directly correlates to the absolute configuration of the ligand proline module.[22,23] For example, when comparing ligands **1a** and **2** that differ only in the configuration of the proline module, a considerable difference in the enantiomeric ratio was observed for both products (Figure 2). The allylation of benzaldehyde was promoted in nearly 90% ee using both ligands (96:4 er and 5.5:94.5 er), but with a different sense of asymmetric induction. A similar effect was also observed for the allylation of acetophenone (68:32 er and 20:80 er). Systematic changes to the configuration of the other chiral centers in the ligand structure had a less significant impact on enantioselectivity. These observations prompted an exploration of the role of the proline module in greater detail.[7]

In order to initiate the investigation, systematic changes to the nature of the carbamate of the proline module were easily explored due to the convergent nature of the synthesis and the ability to modify the size of this group. Ligand **1a**, the optimal diastereomer for benzaldehyde allylation, was chosen as a starting structure into which carbamate modifications were incorporated. Ligands **1b−e** were synthesized from a common precursor (Figure 3), differentiated by the size of the carbamate substituent from a small group (methyl), to a large group (1-adamantyl).[19] The ligands were then evaluated for allylation of an aromatic aldehyde

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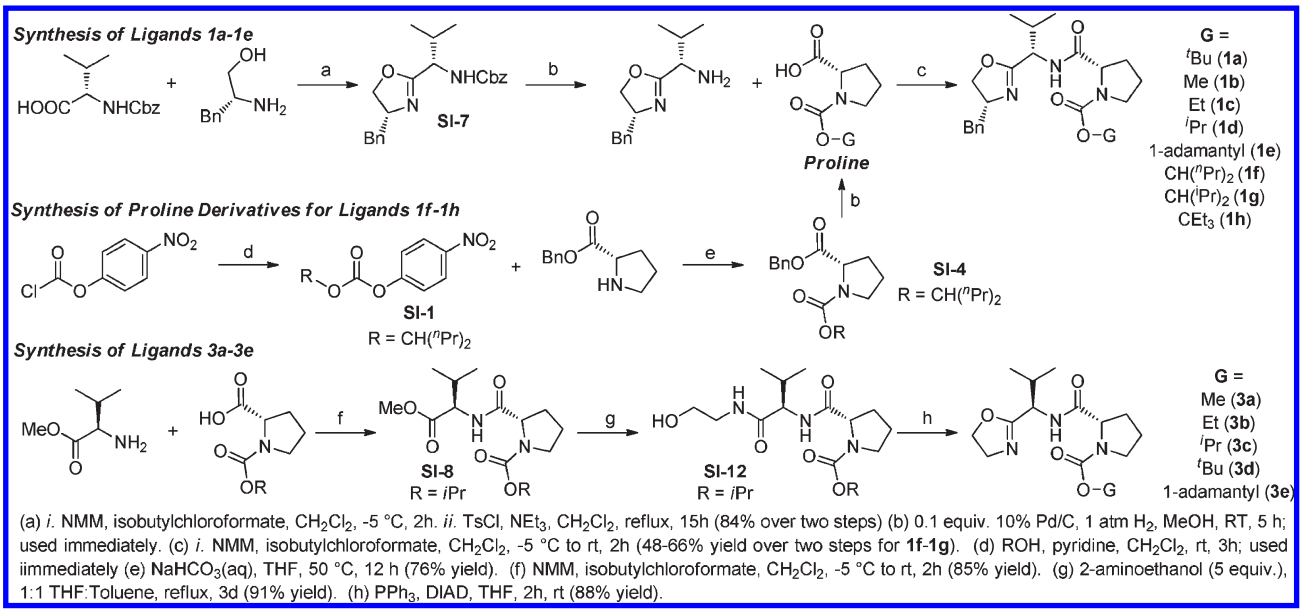
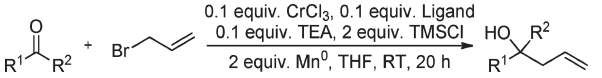


FIGURE 3. Representative syntheses of oxazoline−proline ligands utilized in this study.

TABLE 2. Systematic Evaluation of Proline Carbamate Ligands in Nozaki−Hiyama−Kishi Allylation Reaction with Three Carbonyl Substrates



entry	G	R^1	R^2	er (R/S)[a]	$\Delta\Delta G^{\ddagger}$[b]
1	Me	Ph	H	60:40	0.24
2	Et	Ph	H	65.5:34.5	0.38
3	*i*Pr	Ph	H	82.5:17.5	0.74
4	*t*Bu	Ph	H	96:4	1.86
5	1-adamantyl	Ph	H	96:4	1.86
6	Me	$PhCH_2CH_2$	H	51:49	0.02
7	Et	$PhCH_2CH_2$	H	52.5:47.5	0.06
8	*i*Pr	$PhCH_2CH_2$	H	56.5:43.5	0.16
9	*t*Bu	$PhCH_2CH_2$	H	74:26	0.61
10	1-adamantyl	$PhCH_2CH_2$	H	73.5:26.5	0.60
11	Me	Ph	Me	25:75	−0.65
12	Et	Ph	Me	24:76	−0.68
13	*i*Pr	Ph	Me	37.5:62.5	−0.30
14	*t*Bu	Ph	Me	69:31	0.47
15	1-adamantyl	Ph	Me	72:28	0.56

[a]ER determined by HPLC equipped with a chiral stationary phase. [b]Estimated at 25 °C.

(benzaldehyde), an aromatic ketone (acetophenone), and an aliphatic aldehyde (hydrocinnamaldehyde). In all cases, qualitative trends are observed between the relative size of the carbamate substituents and the product enantioselectivity (Table 2). The range is noteworthy for the allylation of benzaldehyde (entries 1−5) in that an er of 60:40 was observed for the methyl substituent (entry 1) versus an er of 96:4 for the 1-adamantyl substituent (entry 5), and a similar, but less severe, trend is observed for the allylation of hydrocinnamaldehyde. A less obvious trend is observed for the allylation of acetophenone in that a change in facial selectivity was found (entries 11−15) when progressing from smaller to larger substituents. A similar magnitude of

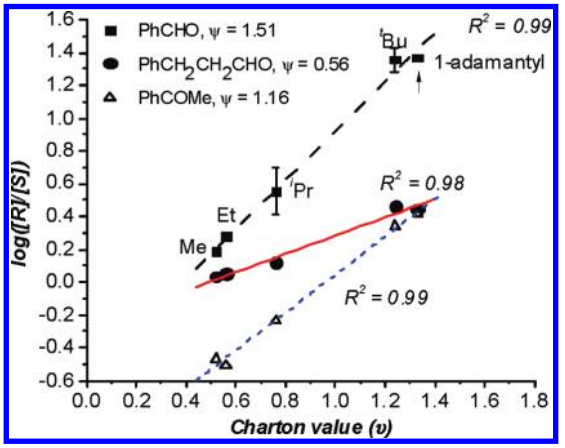


FIGURE 4. Plot of enantiomeric ratio versus Charton values in the enantioselective allylation of three carbonyl substrates.

asymmetric induction for the catalyst containing the smallest group **1a** and the largest group **1e** was measured, albeit with the opposite facial selection. Additionally, it is interesting to inspect the calculated $\Delta\Delta G^{\ddagger}$values wherein the addition of one methyl group (entries 3 and 4) changes this value ~1.1 kcal/mol.

Considering that an enantiomeric ratio is (by definition) the relative rate of the formation of two enantiomers from a pro-chiral substrate (for kinetically controlled reactions), correlating steric parameters to the log of enantiomeric ratio ($\log(R/S) = \psi\upsilon$) is possible.[24] Excellent correlations for the allylation of benzaldehyde, acetophenone, and hydrocinnamaldehyde are observed using either Charton or Taft values (Figure 4, only Charton values depicted). The sensitivity (ψ) is the greatest for benzaldehyde indicating that changing the size of the carbamate substituent has the greatest impact on enantioselectivity as compared to the other substrates

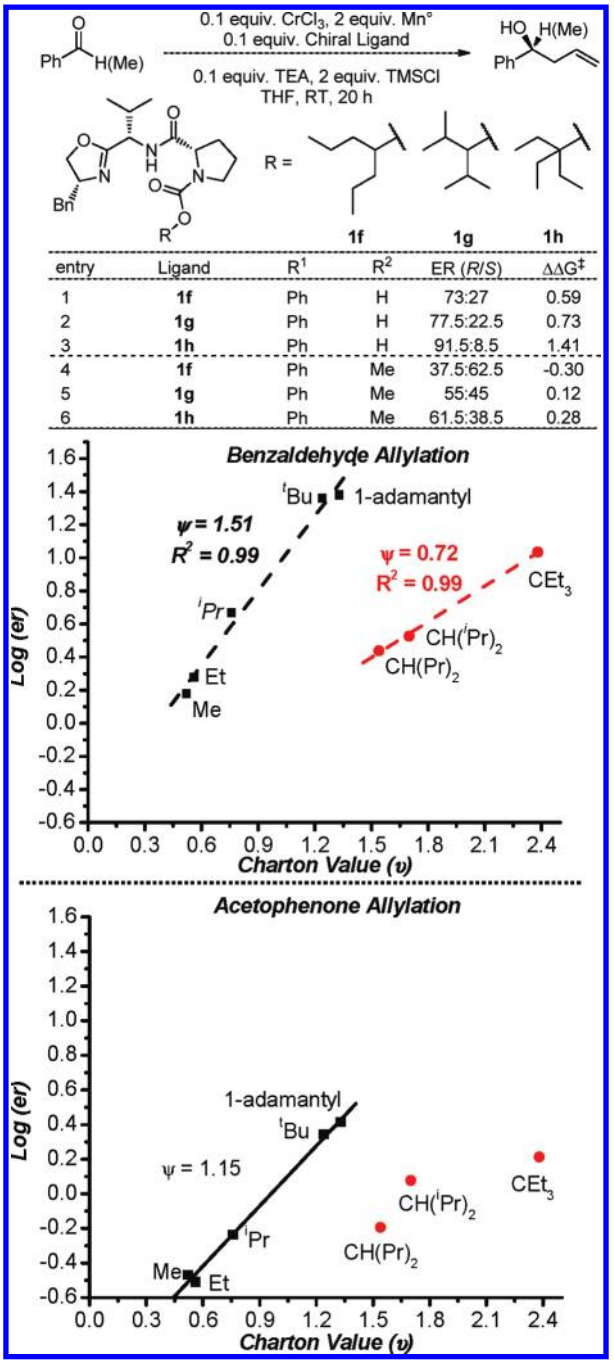
(24) It should also be noted that k_{rel} values or selectivity factors derived from kinetic resolutions should also be able to be correlated. Additionally, $\Delta\Delta G^{\ddagger}$ can be used in the correlation.

evaluated. The observation of linear free energy relationships is of great interest in that it implicates that only one structural perturbation to the diastereomeric transition state occurs upon a systematic change.

A main question that arises from this observation is what is the structural origin of this relationship? Unfortunately, we have been unable to structurally characterize the ligated Cr complex which would aid in the development of a predictive stereochemical model and allow for comparison to the observed LFER.[25] Therefore, our attention has been directed toward three questions: (1) Can this correlation be utilized to predict the outcome of a proposed catalyst? (2) Can we extend the steric parameter analysis to a related catalyst developed in our laboratory? (3) Can we re-evaluate previously reported enantioselective processes using this correlation? The following sections discuss our efforts to explore these questions.

Synthesis of New Catalysts for the NHK Allylation. When analyzing the LFER described above, larger substituents on the carbamate could provide for higher enantioselectivity if the relationship remained linear. This would depend on whether any global structural changes occurred upon making further systematic changes. The linear fits of the Charton plots for each substrate can be extrapolated to a given Charton value with the largest substituent of CEt_3 predicted to achieve exceptionally high enantioselection for benzaldehyde allylation (Figure 5). With this in mind, catalysts **1f**−**h** were synthesized and subsequently evaluated in the allylation of benzaldehyde (entries 1−3) and acetophenone (entries 4−6). To our surprise, these catalysts performed considerably poorer than the previous optimal catalyst **1a** with a *tert*-butyl or catalyst **1e** with an adamantyl carbamate. However, plotting these results shows that these substantially larger groups can be fit linearly with a different ψ value (0.72 versus 1.51, benzaldehyde allylation) with a break in the plot (Figure 5). As is seen in Hammett analysis where a break can indicate a change in mechanism,[4,26] the break in the Charton plot suggests a change in the catalyst conformation. The linearity following the break again indicates only one change is occurring by modifying the carbamate group with these larger groups to achieve the new LFER. While the initial desire was to predict the outcome of these catalysts, this study serves as evidence of the carbamate group impact on catalyst conformation and thus the enantioselectivity. Even without structural characterization of the catalyst, this information should aid in the construction of a stereochemical model for this complex system.

Charton Analysis of Optimal Ligand for Ketone Allylation. As briefly mentioned above, we have recently reported the first highly enantioselective catalytic ketone allylation of aromatic ketones using allylic halides.[23] Our use of a modular ligand facilitated the discovery of a truncated ligand **3a** responsible for the effectiveness of this system. Based on the initial success with the Charton analysis for the optimal ligand for benzaldehyde allylation, we explored the analogous series with the truncated ligand. Ligands **3a**−**e**, lacking an oxazoline substituent, were synthesized. These ligands were evaluated in both benzaldehyde and acetophenone allylation (Figure 6). Again plotting log of enantiomeric ratio versus Charton values leads to a LFER for both carbonyl substrates (Figure 6). In contrast to ligands **1a**−**e**, a significantly larger ψ value is observed for acetophenone allylation (1.88) in comparison to benzaldehyde allylation (0.58). The high sensitivity for acetophenone allylation is highlighted by the er range of 0.28 to 10.1 (57% ee (*S*) to 82% ee (*R*)) whereas benzaldehyde allylation has an er range of 5.3 to 19 (68% ee to 90% ee). The oxazoline module has



entry	Ligand	R^1	R^2	ER (*R*/*S*)	$\Delta\Delta G^{\ddagger}$
1	**1f**	Ph	H	73:27	0.59
2	**1g**	Ph	H	77.5:22.5	0.73
3	**1h**	Ph	H	91.5:8.5	1.41
4	**1f**	Ph	Me	37.5:62.5	-0.30
5	**1g**	Ph	Me	55:45	0.12
6	**1h**	Ph	Me	61.5:38.5	0.28

FIGURE 5. Use of larger ligand substituents in the NHK allylation of benzaldehyde and acetophenone and the corresponding Charton plots.

(25) We have kinetic evidence that the reaction is first order in [catalyst], and we observe no nonlinear effects but have been unable to determine a precise stereochemical model due to the number of possible orientations of ligand/substrates/counterions about Cr.

(26) For an example, see: Richards, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689–4691.

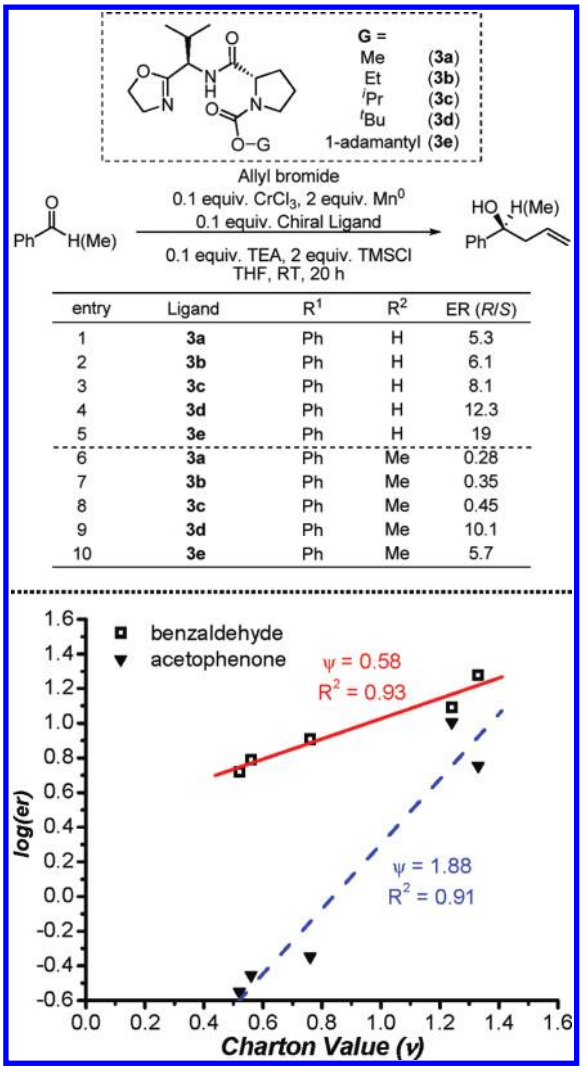


FIGURE 6. Evaluation of analogues of the optimal ligand for ketone allylation and resulting Charton analysis.

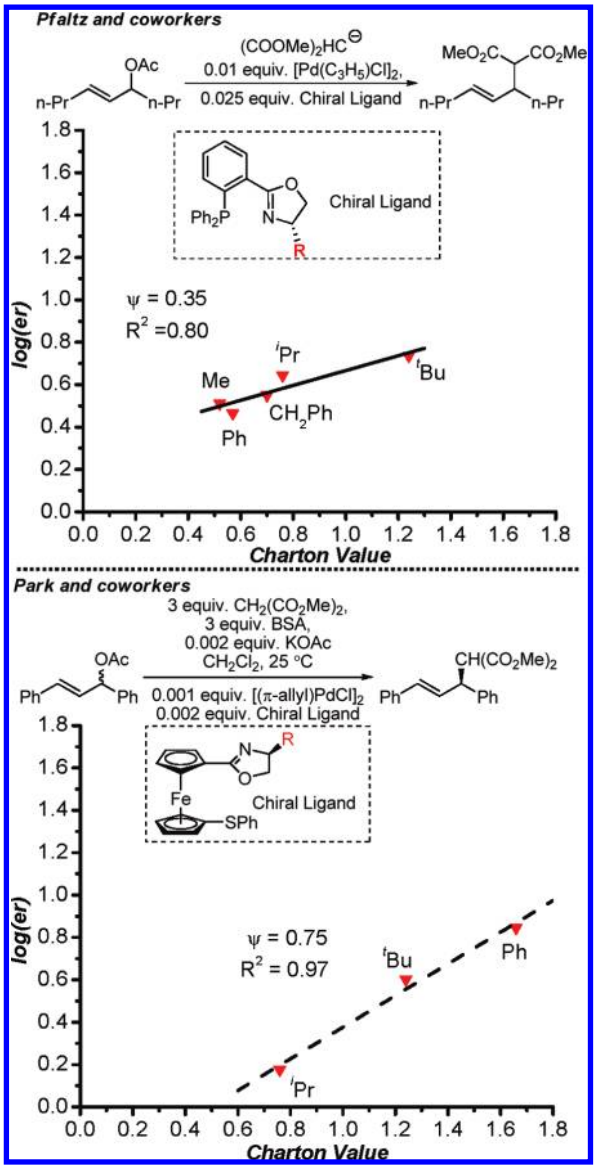


FIGURE 7. Charton analysis of Pd-catalyzed allylic alkylation reactions with oxazoline-based ligands.

an unanticipated impact in how the substrates interact with the catalyst as suggested by the differences in substrate sensitivity for each catalyst class. Even with the significant modifications to the structure of this catalyst as compared to **1a**, a high enantioselectivity can be achieved for benzaldehyde allylation with catalyst **3e** containing the adamantyl carbamate. Catalyst **3e** is poorer than the original optimal catalyst **3d** for acetophenone allylation suggesting that a potential break may be occurring in this Charton plot as larger substituents are incorporated. Considering this ligand structure has a diastereomeric relationship between the proline and amide module as compared to catalyst **1a**, the ability to extend the Charton analysis is notable.

Successful Correlation of Previously Reported Asymmetric Catalytic Reactions. An important consideration is whether the Charton analysis described herein is limited to only one set of ligands/reactions. To evaluate this, various reactions types and ligand structures in previously reported enantioselective processes were treated using Charton analysis. In general, reactions performed using a range of ligand modifications were chosen for analysis and it should be noted that the analyses presented below are only illustrative, not comprehensive. Finally, at the end of this section, we will present some of the unusual sets of data evaluated which illustrate some of the potential limitations of the method.

Positive ψ Values: Where Larger Substituents Lead to Better Selectivity. The seminal report by Pfaltz concerning the use of phosphine oxazoline ligands, a highly useful and modular ligand class, in asymmetric Pd-catalyzed allylic alkylation reactions was evaluated (Figure 7).[27] We found that the size of the ligand substituent on the oxazoline can be correlated to product enantiomeric ratio with a modest ψ = 0.35. This implicates that only substantial changes to the group off the oxazoline will result in a significantly improved enantiomeric ratio. Also, it should be noted that the Ph substituent has two values (Table 1), and the smaller value (0.57) was utilized. This will be discussed further below. A similar correlation was found when Park and co-workers'

(27) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568.

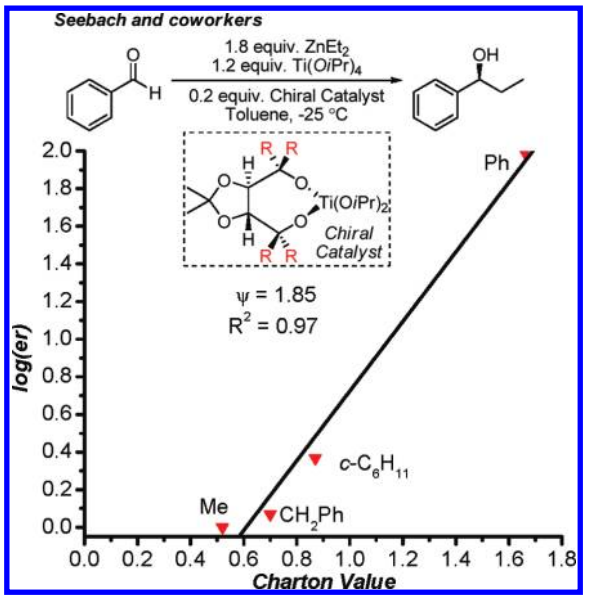


FIGURE 8. Charton analysis of diethylzinc additions to benzaldehyde using TADDOL-based ligands.

reported use of a chiral 1′-substituted oxazolinylferrocene as a chiral ligand for an analogous reaction was analyzed.[28] The change in enantiomeric ratio as a factor of steric size was more pronounced in this ligand class, which is indicated by the larger ψ value (0.75).

Exploring other asymmetric organometallic reactions also proved fruitful, where a LFER is observed for Seebach and co-workers' reported asymmetric addition of diethyl zinc to benzaldehyde, catalyzed by chiral Ti-TADDOL derivatives (Figure 8).[29] In this case, a substantial ψ value (1.85) indicates that this reaction is highly sensitive to the nature of the ligand substituents. Also, it should be noted that the larger value for Ph is used in this case ($\nu = 1.66$).

Negative ψ Values: Where Smaller Subtituents Lead to Greater Selectivity. Chiral hydroxamic acids were also found to correlate well (Figure 9) as demonstrated by Uang and co-workers for the asymmetric epoxidation of allylic alcohols using Vanadium salts.[30] However, in this case the ψ value is negative, consistent with a smaller ligand substituent leading to higher enantiomeric ratio. This is in contrast to the common conception that bigger substituents are generally better in ligand structure. Two other examples are presented to illustrate a negative ψ value. The first is Imamoto and co-workers' reported enantiomeric ratios for the asymmetric hydrogenation of α-(acylamino)acrylic derivatives, catalyzed by chiral Rh-BisP* complexes (Figure 9)[31] wherein the range of Charton values in this correlation (ν = 0.87−2.38) is noteworthy. The second is the enantioselective cyclopropanation of allylic alcohols with bis(sulfonamide) derived chiral diamines and bis(halomethyl) zinc reagents reported by Denmark and co-workers (Figure 9).[32] Again, a linear correlation in the Charton plot was observed wherein the reaction outcome is highly sensitive to the nature of the substituent size as indicted by a large magnitude ψ value (−1.8).

Substrate Effects. Correlating the size of the substrate to product enantiomeric ratio is possible, especially considering that the origin of Taft/Charton values is based on the effect of substituent size on the rate of ester hydrolysis. For example, the enantioselective aziridination of styrenes with Mn−Salen complexes reported by Komatsu[33] was analyzed wherein styrene has a significantly lower enantiomeric ratio than substrates with substitution *trans* in the β-position (Figure 10). An excellent correlation of the size of the group in the β-position of the styrene was observed where a ψ value of 1.42 was calculated, indicating that in this case a larger substituent leads to a better outcome.

The report by Zhou and co-workers using chiral 1,2,3,4-tetrahydroquinolinyloxazoline ligands in the Ru-catalyzed asymmetric transfer hydrogentation of ketones was analyzed (Figure 10).[34] Excitingly, both the substituents on the ligand and the ketone substrate could be correlated leading to linear free energy relationships. Of interest, a significant negative ψ value is observed for the substrate indicating that smaller substrates perform better and a modest positive ψ value is found for the ligand.

Potential Issues/Limitations of Charton Analysis. Considering Charton values were established for the rate of methyl ester hydrolysis, which can be considered a mechanistically simple reaction, it is exciting that direct application to asymmetric catalysis was successful. However, as with any type of LFER, there are issues and limitations that one must consider when implementing this tool. Below are examples to demonstrate some of the common limitations we found in our investigations.

Complexity Associated with Phenyl Groups. Unlike acid-catalyzed methyl ester hydrolysis, asymmetric catalysis can be influenced by electronic factors, such as π-stacking, which were not viable concerns in Taft's original work. As mentioned above, this is observed in the fact that two Charton values exist for Ph, 1.66 and 0.57. These two values are believed to originate for the in-plane and out-of-plane orientations of the phenyl group to the carbonyl. The in-plane orientation (0.57) would offer very little steric repulsion to any incoming nucleophile to the carbonyl. If the phenyl group is placed out-of-plane or perpendicular to the carbonyl (1.66), the steric effect is greatly increased as the nucleophile approaches the carbonyl, which could account for the slower rate of hydrolysis. As demonstrated above, it is common to have to check if each of these values when using Charton correlations, and one can imagine that this conflict in calculated values can sometimes result in unexplained lack of correlation of the Ph group.

Other Unusual Observations. In addition to Ph, there are a number of substituents that have questionable Charton values. Analyzing the steric bulk of ^{n}Pr, ^{n}Bu, and ^{i}Bu

(28) Park, J.; Quan, Z.; Lee, S.; Han Ahn, K.; Cho, C.-W. *J. Organomet. Chem.* **1999**, *584*, 140–146.
(29) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuehnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2110.
(30) Wu, H.-L.; Uang, B.-J. *Tetrahedron: Asymmetry* **2002**, *13*, 2625–2628.
(31) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636.
(32) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219–2222.
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(34) Zhou, Y.-B.; Tang, F.-Y.; Xu, H.-D.; Wu, X.-Y.; Ma, J.-A.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 469–473.

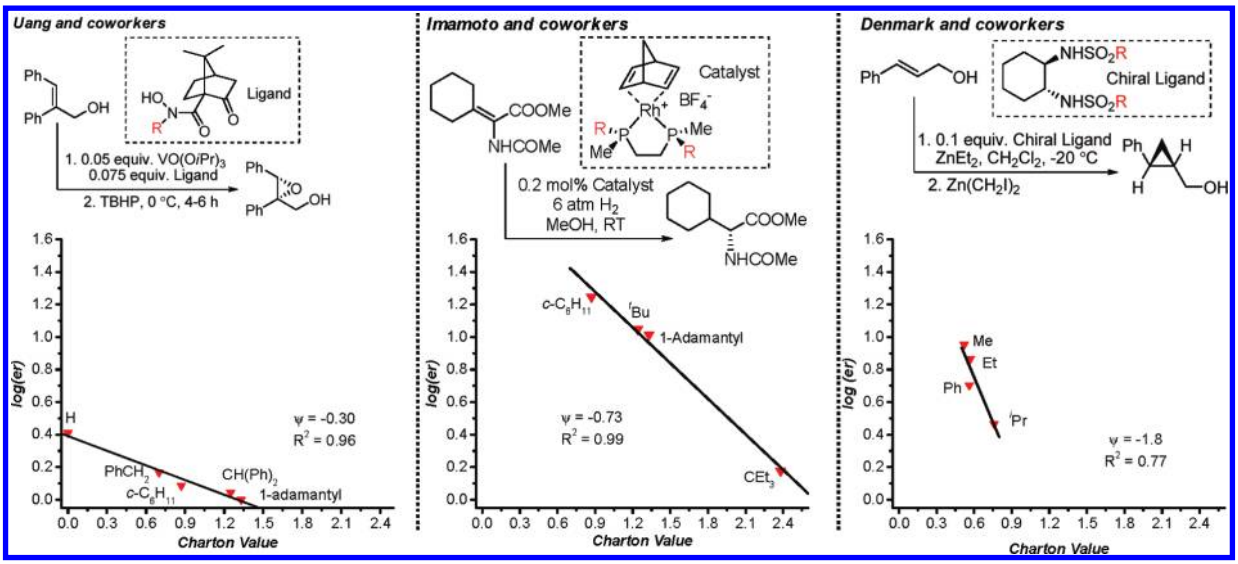

FIGURE 9. Charton analysis of various reaction types wherein a negative ψ value is observed.

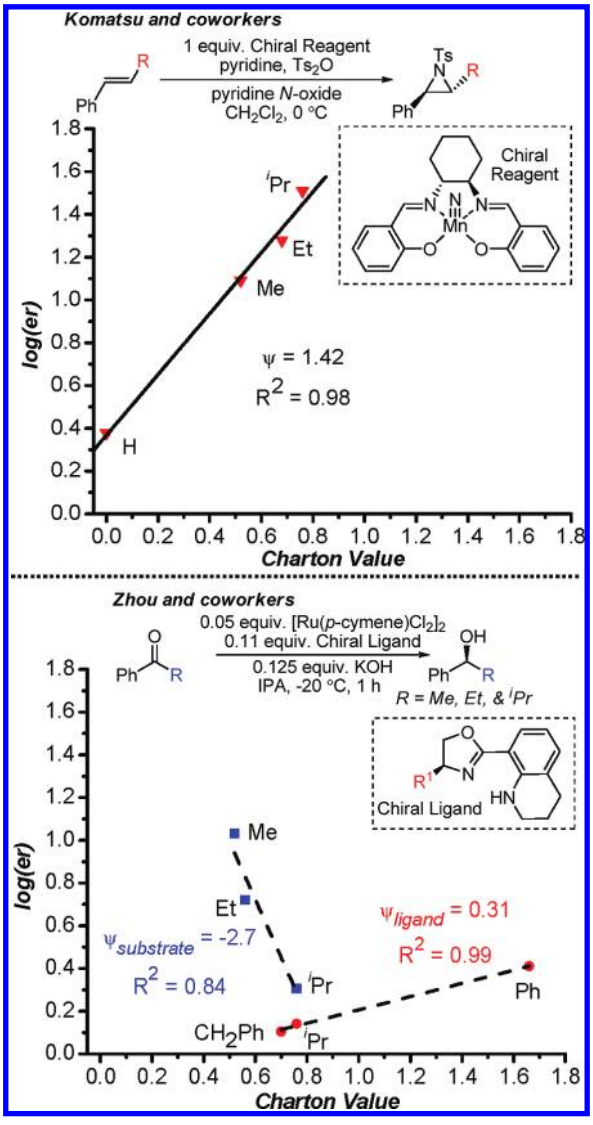

FIGURE 10. Charton analysis in the effect of substrate size on the enantioselective outcome.

substituents, we consider ^{i}Bu to occupy more volume than ^{n}Pr or ^{n}Bu. Surprisingly, all three substituents have a Charton value of 0.68.[12] Considering that these values were calculated for the attack of a nucleophile on the carbonyl of a methyl ester substrate this can be rationalized, as all three groups contain a methylene carbon α to the carbonyl. When attempting to employ these substituents in correlations a nonlinear dependence can result. Charton analysis of the report by Braga and co-workers' asymmetric addition of diethylzinc to aldehydes reveals an example of nonlinearity (Figure 11).[35] We found that a good correlation is observed for the ^{n}Pent, ^{n}Hex, ^{n}Hep, and ^{i}Pr substrates only if the ^{n}Bu substrate was excluded. It is difficult to rationalize why this substrate deviates to such a large degree but again highlights the complex nature of asymmetric catalysis. As an aside, Charton analysis of the effect of the ligand substituent reveals a LFER with a ψ value of -0.59.

"Break" in the Charton Plot. A break in the Charton plot can also occur as demonstrated in our chemistry described above where we attribute this to a change in ligand conformation. A similar result is observed by conducting a Charton analysis on the chiral oxazoline-based ligand used by Brunner and co-workers in their Rh-catalyzed asymmetric hydrosilylation reaction (Figure 12).[36] A linear free energy relationship is observed for five substituents with a ψ value of 0.48 only when the ^{t}Bu substituent is excluded from the analysis. One possible explanation for the significant difference is the substituent size forces the chelation environment about Rh to change where the change may result in the ligand slipping from bidentate to monodentate. On this issue, one must be very careful in analysis of limited data sets. While we present a few examples above with only three data points, the conclusions that arise from such a data set must be taken very carefully, and it is suggested that either substrates with a broad range of Charton values

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(36) Brunner, H.; Stoeriko, R. *Eur. J. Inorg. Chem.* **1998**, 783–788.

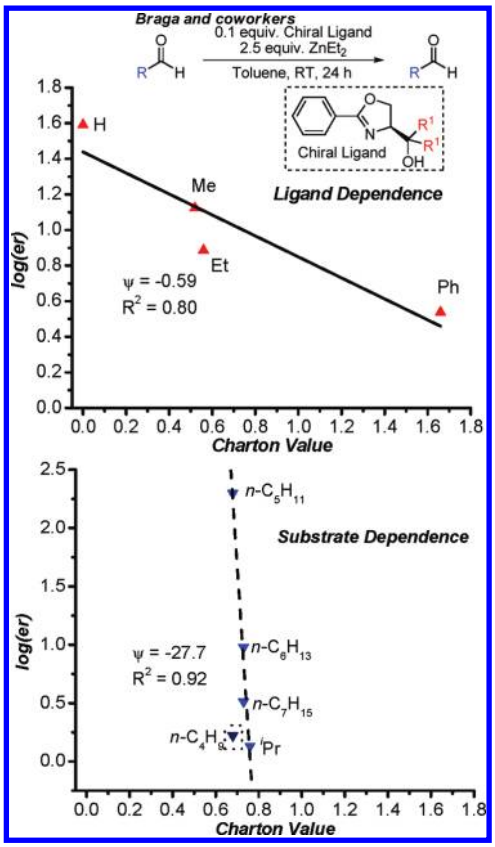

FIGURE 11. Charton analysis of a diethylzinc addition to aldehyde derivatives using an oxazoline-derived ligand.

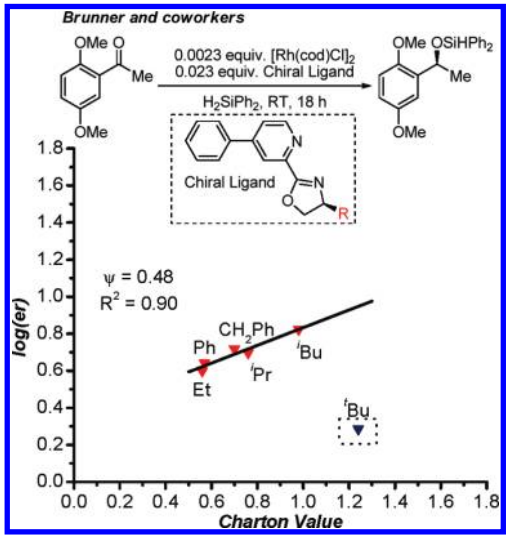

FIGURE 12. Charton analysis of a hydrosilylation reaction of substituted benzaldehyde derivatives using a pyridyl−oxazoline ligand.

or a significant number of substrates with a limited range of Charton values are evaluated to achieve statistically robust results.

Conclusions

In summary, we have applied steric parameters originally developed by Taft to quantitatively analyze asymmetric catalytic processes through linear free energy relationships. To this end, we have illustrated that linear free energy relationships can be constructed by plotting log of enantiomeric ratio versus Charton steric parameters for multiple substrates using modular oxazoline ligands developed in our laboratory for aldehyde and ketone allylation under NHK conditions. In an attempt to design an improved catalyst for carbonyl allylation, we found incorporation of a larger group into our ligand structure resulted in an unanticipated break in the linearity of the Charton plot. Interestingly, a new LFER is observed after the break most likely indicating the size of the substituent forces the catalyst to adopt a different conformation or constitution.

We have also been able to extend the Charton analysis to the optimal catalyst for ketone allylation under NHK conditions developed in our laboratory where, in this case, the sensitivity as measured by the ψ value is greatest for the allylation of acetophenone in comparison to benzaldehyde. This is contrast to ligand **1a**. While understanding the origin of these effects is of great importance, the LFER observed for these catalysts will be clearly central as we utilize this ligand class in optimizing catalysts for difficult substrate classes and extending it to new reaction development.

Finally, we have investigated the use of Charton analysis for previously reported enantioselective processes. LFERs can be successfully observed for a wide variety of ligands and reaction types indicating the potential broad applicability of the quantitative use of steric parameters in asymmetric catalyst design. It should be pointed out that issues exist in terms of the accuracy of some of the Charton values. However, in our opinion, insight can be garnered not only from the successful correlations but also from the outliers. Future work in our laboratory is focused on applying the quantitative use of steric parameters to aid in the design of improved and new catalysts for asymmetric catalytic reactions as well as understanding the structural and mechanistic origins of the observed linear free energy relationships.

Experimental Section

Preparation of Heptan-4-yl 4-Nitrophenyl Carbonate (SI-1). To a stirring solution of 4-heptanol (495 μL, 4.26 mmol, 1 equiv), CH_2Cl_2 (10 mL), and pyridine (520 μL, 6.39 mmol, 1.5 equiv) at −5 °C was added *p*-nitrophenyl chloroformate (1.03 g, 5.11 mmol, 1.2 equiv) in four equal portions. The reaction flask was removed from the cooling bath and allowed to warm to room temperature with stirring. After the reaction mixture was stirred for 3 h, the precipitated pyridine hydrochloride salt was removed by filtration; H_2O (15 mL) was added to the filtrate, and the solution was extracted with Et_2O (3 × 30 mL). The organics were washed with 1 M HCl (3 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and saturated aqueous NaCl (30 mL). The organics were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude mixture was taken on without further purification: R_f = 0.68 (33% EtOAc/hexanes, stained with $KMnO_4$).

Preparation of (*S*)-2-Benzyl 1-Heptan-4-ylpyrrolidine-1,2-dicarboxylate (SI-4). To a stirring solution of **SI-1** (1.11 g, 3.96 mmol, 1.1 equiv), THF (6 mL), and saturated aqueous $NaHCO_3$ (6 mL) was slowly added Bn-Pro-OH (870 mg, 3.6 mmol, 1 equiv) in three equal portions. The reaction mixture was then heated to 50 °C. After being stirred for 12 h, the mixture was concentrated under reduced pressure to remove THF. The resulting mixture was then extracted with CH_2Cl_2 (3 × 40 mL). In order to remove the residual *p*-nitro phenol, the organics were

washed repeatedly with 10% aqueous $NaHCO_3$ until the yellow color did not persist. The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3.5 × 13 cm column, eluting with 8% EtOAc/hexanes, collecting 9 mL fractions. The product-containing fractions were combined and concentrated under reduced pressure to give the desired product **SI-4** (950 mg, 76% yield) as a clear viscous oil: R_f = 0.47 (33% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ −38.2 (c = 0.55, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 7.36−7.29 (m, 5H), 5.26−5.00 (m, 2H), 4.85−4.70 (m, 1H), 4.49−4.27 (m, 1H), 3.65−3.36 (m, 2H), 2.31−2.10 (m, 1H), 2.05−1.77 (m, 3H), 1.63−1.16 (m, 8H), 0.96−0.79 (m, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 172.7, 154.5, 135.8, 128.5, 128.2, 127.9, 75.0, 66.5, 58.8, 46.7, 36.4, 30.9, 23.4, 18.4, 13.9; IR (neat) 2957, 2934, 2873, 1746, 1698, 1406, 1336, 1162, 1114, 1086, 982, 737, 696 cm^{-1}; HRMS (ES) calcd. $C_{20}H_{29}NO_4Na$ (M + Na)$^+$ 370.1994, obsd. 370.1995.

Preparation of Benzyl (*S*)-1-((*R*)-4-Benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamate (SI-7). To a stirring solution of Cbz-Val-OH (2.06 g, 8.19 mmol, 1 equiv) and CH_2Cl_2 (33 mL), at −5 °C, was slowly added *N*-methylmorpholine (1.08 mL, 9.83 mmol, 1.2 equiv) via syringe. After the solution was stirred for 10 min at −5 °C, isobutyl chloroformate (1.08 mL, 8.19 mmol, 1.0 equiv) was added dropwise, via syringe, to the reaction mixture. After the solution was stirred for an additional 45 min at −5 °C, H-D-phenylalaninol (1.36 g, 8.99 mmol, 1.1 equiv) was added in ca. three equal portions to the reaction mixture. The reaction mixture was then allowed to warm to room temperature. After 2 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (15 mL) and diluted with CH_2Cl_2 (40 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with H_2O (3 × 20 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude mixture was taken on without further purification.

To a stirring solution of the crude mixture in CH_2Cl_2 (60 mL) and triethylamine (40 mL), at −5 °C, was slowly added *p*-toluenesulfonyl chloride (1.85 g, 9.83 mmol, 1.2 equiv) in ca. three equal portions. After addition was complete, the flask was removed from the cooling bath and the reaction mixture was allowed to warm to room temperature. After ca. 45 min, TLC analysis indicated complete conversion of the starting material to the *p*-toluenesulfonate. The reaction mixture was heated at reflux for 15 h. The reaction mixture was allowed to cool to room temperature before diluting with CH_2Cl_2 (25 mL). To this mixture was slowly added saturated aqueous $NaHCO_3$ (25 mL). The resulting organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), H_2O (20 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4.75 × 13 cm column, eluting first with 300 mL of 50% Et_2O/hexanes, followed by 35% acetone/hexanes, collecting 18 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired Cbz protected oxazoline amine (2.52 g, 84% yield over two steps) as a white solid: mp 96−98 °C; R_f = 0.57 (35% acetone/hexanes, stained with phosphomolybdic acid); $[\alpha]^{23}_D$ −11.7 (c = 0.325, $CHCl_3$); 400 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 7.37−7.17 (m, 10H), 5.39 (d, J = 8.8 Hz, 1H), 5.15 (d, J = 12.3 Hz, 1H), 4.44−4.35 (m, 2H), 4.23 (t, J = 8.8 Hz, 1H), 4.00 (t, J = 8.0 Hz, 1H), 3.08 (dd, J = 13.7, 5.1 Hz, 1H), 2.63 (dd, J = 13.7, 8.4 Hz, 1H), 2.11 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); 100 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 166.7, 156.1, 137.6, 136.4, 129.2, 128.5, 128.4, 128.1, 128.0, 126.5, 72.2, 67.0, 66.9, 54.3, 41.7, 31.5, 18.8, 17.4; IR (thin film) 2977, 2935, 2863, 1382, 1123 cm^{-1}; HRMS (ES) calcd. $C_{22}H_{27}N_2O_3$ (M + H)$^+$ 367.2022, obsd. 367.2019.

Preparation of (*S*)-Heptan-4-yl 2-((*S*)-1-((*R*)-4-Benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (1f). To a stirring solution of (*S*)-1-((heptan-4-yloxy)carbonyl)pyrrolidine-2-carboxylic acid (obtained by deprotection of the **SI-4** with 10 mol % Pd/C at 1 atm H_2 for 5 h) (141 mg, 0.55 mmol, 1 equiv) and CH_2Cl_2 (3 mL), at −5 °C, was slowly added *N*-methylmorpholine (72 μL, 0.66 mmol, 1.2 equiv) via syringe. After the solution was stirred for 20 min at −5 °C, isobutyl chloroformate (72 μL, 0.55 mmol, 1.0 equiv) was added dropwise, via syringe, to the reaction mixture. After the solution was stirred for an additional 45 min at −5 °C, the free oxazoline amine (140 mg, 0.60 mmol, 1.1 equiv), obtained by deprotection of the **SI-7** shown above (10 mol % Pd/C at 1 atm H_2 for 5 h), was added dropwise to the reaction mixture as a solution in CH_2Cl_2 (0.5 mL). The reaction mixture was then allowed to warm to room temperature. After 3 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (1 mL) and diluted with CH_2Cl_2 (6 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with H_2O (3 × 5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 × 15 cm column, eluting first with 200 mL of 50% EtOAc/hexanes, followed by 40% acetone/hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired ligand (119 mg, 46% yield) as a clear colorless oil: R_f = 0.30 (66% EtOAc/hexanes, stained with PMA); $[\alpha]^{23}_D$ −36.7 (c = 0.39, $CHCl_3$); 400 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 7.29 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 6.8 Hz, 2H), 4.83 (t, J = 5.6 Hz, 1H), 4.57 (dd, J = 8.6, 5.6 Hz, 1H), 4.42−4.29 (m, 2H), 4.20 (t, J = 8.8 Hz, 1H), 3.97 (t, J = 8.2 Hz, 1H), 3.58−3.33 (m, 2H), 3.12 (dd, J = 13.9, 5.1 Hz, 1H), 2.62 (dd, J = 13.9, 8.9 Hz, 1H), 2.44−1.80 (m, 4H), 1.63−1.21 (m, 7H), 0.97−0.85 (m, 14H); 100 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 171.4, 166.3, 156.3, 137.8, 129.3, 128.5, 126.5, 75.6, 72.1, 67.1, 60.3 52.4, 46.9, 41.7, 36.6, 31.6, 27.8, 24.5, 18.5, 17.7, 14.0; IR (neat) 3314, 2958, 2933, 2872, 1690, 1664, 1533, 1412, 1190, 1116, 982, 702 cm^{-1}; HRMS (ES) calcd $C_{27}H_{41}N_3O_4Na$ (M + Na)$^+$ 494.2995, obsd 494.2990.

Preparation of (*S*)-Isopropyl 2-((*R*)-1-methoxy-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-8). To a stirring solution of (*S*)-1-(isopropoxycarbonyl)pyrrolidine-2-carboxylic acid (103 mg, 0.51 mmol, 1 equiv) in CH_2Cl_2 (2 mL), at −5 °C, was slowly added *N*-methylmorpholine (84 μL, 0.76 mmol, 1.5 equiv) via syringe. After the solution was stirred for 20 min at −5 °C, isobutyl chloroformate (67 μL, 0.51 mmol, 1 equiv) was added dropwise, via syringe, to the reaction mixture. After the solution was stirred for an additional 30 min at −5 °C, *N*-methylmorpholine (64 μL, 0.58 mmol, 1.15 equiv) was added slowly, via syringe, to the reaction mixture. This was followed by the addition of *R*-valine methyl ester hydrochloride (94 mg, 0.56 mmol, 1.1 equiv) in ca. three equal portions to the reaction mixture. The reaction mixture was then allowed to warm to room temperature. After 2 h, TLC analysis indicated complete consumption of starting material. The reaction was quenched by addition of 1 M HCl (5 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated, and the aqueous layer was removed. The organic layer was washed with H_2O (3 × 10 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by mixed solvent recrystallization (1:4, Et_2O/hexanes) to yield **SI-8** as colorless crystals (138 mg, 86% yield): mp 85−86 °C; R_f = 0.40 (66% EtOAc/hexanes, stained with $KMnO_4$); $[\alpha]^{23}_D$ −81.8 (c = 2.89, $CHCl_3$);

500 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 4.96 (pent, J = 6.3 Hz, 1H), 4.53 (dd, J = 8.8, 4.9 Hz, 1H), 4.36 (d, J = 7.8 Hz, 1H), 3.72 (s, 3H), 3.57−3.36 (m, 2H), 2.35−1.84 (m, 5H), 1.27 (t, J = 5.4 Hz, 6H), 0.96 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 172.3, 172.1, 155.9, 69.4, 60.8, 57.2, 52.0, 47.2, 30.8, 29.4, 24.2, 22.3, 19.1, 17.8; IR (neat) 3262, 3070, 2973, 1742, 1710, 1659, 1552, 1412, 1202, 1176, 1143, 1122, 768 cm^{-1}; HRMS (ES) calcd $C_{15}H_{27}N_2O_5$ $(M + H)^+$ 315.1920, obsd 315.1919.

Preparation of (*S*)-Isopropyl 2-((*R*)-1-(2-Hydroxyethylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (SI-12). To a stirring solution of **SI-8** (141 mg, 0.45 mmol, 1 equiv), toluene (800 μL), and tetrahydrofuran (800 μL) was added 2-aminoethanol (137 μL, 2.28 mmol, 5 equiv) via syringe. After 3 d at reflux the mixture was diluted with $CHCl_3$ (10 mL). The organic layer was then washed with H_2O (3 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by mixed solvent recrystallization (1:5 CH_2Cl_2/hexanes) to yield a white solid (141 mg, 91% yield): mp 185−187 °C; R_f = 0.43 (10% MeOH/CH_2Cl_2, $KMnO_4$); $[\alpha]^{23}_D$ +1.6 (c = 0.49, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 4.52 (dd, J = 8.8, 4.9 Hz, 1H), 4.32 (d, J = 5.9 Hz, 1H), 3.72 (s, 3H), 3.53−3.32 (m, 2H), 2.34−1.81 (m, 14H), 1.66 (bs, 6H), 0.97 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 172.4, 80.5, 60.6, 57.3, 52.1, 47.3, 42.0, 36.3, 31.2, 30.6, 24.2, 19.2, 17.9; IR (neat) 3285, 2966, 2872, 1664, 1638, 1546, 1421, 1383, 1345, 1231, 1173, 1109, 930, 768 cm^{-1}; HRMS (ES) calcd $C_{16}H_{29}N_3O_5Na$ $(M + Na)^+$ 366.2005, obsd 366.2005.

Preparation of (*S*)-Isopropyl 2-((*R*)-1-(4,5-Dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (3c). To a stirring solution of **SI-12** (117 mg, 0.34 mmol, 1 equiv) and tetrahydrofuran (2.25 mL) was added triphenylphosphine (108 mg, 0.41 mmol, 1.2 equiv) in one portion. This was followed by dropwise addition of diisopropyl azodicarboxylate (86 μL, 0.41 mmol, 1.2 equiv), via syringe, to the reaction mixture. The reaction mixture was allowed to clear between drops. The progress of the reaction was monitored by TLC analysis. After 2 h of stirring, the mixture was concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 1.5 × 12 cm column, eluting with 75 mL or 35% EtOAc/hexanes followed by 40% acetone/hexanes, collecting 9 mL fractions. The product-containing fractions were combined and concentrated under reduced pressure. The solid was then recrystallized by mixed solvent recrystallization (1:4 acetone/hexanes) to yield a colorless solid (97 mg, 88% yield): mp 112−114 °C; R_f = 0.31 (50% acetone/hexanes, ninhydrine); $[\alpha]^{23}_D$ −71.7 (c = 0.29, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) at 50 °C δ 4.88 (sept, J = 6.3 Hz, 1H), 4.54 (dd, J = 8.8, 4.9 Hz, 1H), 4.34−4.25 (m, 1H), 4.20 (sext, J = 9.3 Hz, 2H), 3.76 (t, J = 9.8 Hz, 2H), 3.53−3.27 (m, 2H), 2.26−1.76 (m, 5H), 1.20 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) at 50 °C δ 172.1, 167.2, 155.9, 69.5, 68.2, 61.2, 54.5, 52.8, 47.5, 31.9, 31.2, 29.7, 24.3, 22.6, 22.5, 19.2, 18.0; IR (neat) 3213, 3045, 2960, 2874, 1687, 1657, 1549, 1418, 1380, 1209, 1110, 933, 769, 697 cm^{-1}; HRMS (ES) calcd $C_{16}H_{27}N_3O_4Na$ $(M + Na)^+$ 348.1899, obsd 348.1908.

Preparation of Homoallylic Alcohols. To a 1.5 dram vial were added $CrCl_3$ (7.9 mg, 0.05 mmol, 0.1 equiv), Mn(0) (325 mesh) (55 mg, 1.0 mmol, 2 equiv), and **2a** (17 mg, 0.05 mmol, 0.1 equiv). The vial was fitted with a permeable Teflon cap, charged with tetrahydrofuran (2.5 mL), and allowed to stir. After ca. 2 min, triethylamine (15 μL, 0.1 mmol, 0.2 equiv) and chlorotrimethylsilane (255 μL, 2 mmol, 4 equiv) were added to the reaction mixture. After the solution had stirred for 20 min and the color had changed to a deep blue/purple color, allyl bromide (85 μL, 1.0 mmol, 2 equiv) was added to the reaction mixture. After 30 min, carbonyl (0.5 mmol, 1 equiv) was added, and the mixture was allowed to stir at room temperature. After 24 h, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (1.5 mL). Caution: Take care to add the $NaHCO_3$ solution dropwise as a large amount of gas evolves. After being stirred for 20 min, the mixture was passed through a Celite plug, eluting with diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 × 15 cm column, eluting with 8% EtOAc/hexanes, collecting 9 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give the desired homoallylic alcohol as a colorless oil (64−97% yield). The enantiomeric excess of acetophenone allylation was determined by HPLC analysis (Chiralcel OJ-H, hexanes/*i*-PrOH = 97/3, flow rate = 1.0 mL/min): t_{major} = 9.6 min (*R*), t_{minor} = 11.5 min (*S*). The enantiomeric excess of benzaldehyde allylation was determined by HPLC analysis (Chiralcel OD, hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{major} = 15.9 min (*R*), t_{minor} = 18.4 min (*S*).[1] The enantiomeric excess of hydrocinnamaldehyde allylation was determined by HPLC analysis (Chiralcel OD, hexanes/*i*-PrOH = 98/2, flow rate = 1.0 mL/min): t_{major} = 19.3 min (*S*), t_{minor} = 34.5 min (*R*).

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Supporting Information Available: Ligand analogue synthesis and ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org