Enantioselectivity

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Quantitatively Correlating the Effect of Ligand-Substituent Size in Asymmetric Catalysis Using Linear Free Energy Relationships**

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In the past three decades, the discovery and application of effective asymmetric catalysts has flourished in both academic and industrial settings.[1] This is especially true within the recent decade where the field of asymmetric catalysis has witnessed an incredible expansion, and the benchmarks for acceptable asymmetric induction have significantly risen. However, the approach to catalyst identification remains mainly empirical, wherein evaluation of a considerable number of catalyst structures is required to develop a mature chiral catalyst. While this process has been expedited by technological advancements,[2] the understanding of the relationship between catalyst structure and the enantioselectivity of the catalyzed reaction is generally precarious. This can be attributed to the small energy differences in the activation barrier leading to the enantiomeric products and/or the complicated preequilibria in most catalytic reactions.[3]

An approach to developing greater predictive power in asymmetric catalysis is based on the use of modular ligands[4] in lieu of a detailed understanding of the microscopic processes involved in asymmetric induction. We believe the ability to make systematic changes to the ligand structure not only leads to enhanced product enantiomeric excess,[5] but allows for the elucidation of structure–enantioselectivity relationships.[6] Herein, we report the use of a modular ligand set to systematically study the effect of ligand size and the first observation of a linear free energy relationship between steric parameters and enantiomeric ratio. Additionally, our analysis of several previously reported enantioselective reactions reveals similar linear free energy relationships.

We have recently disclosed the use of modular oxazoline ligands[7] in enantioselective Nozaki–Hiyama–Kishi reactions of allylic halides[8,9] with both aldehydes[5a] and ketones[5c] (Figure 1). A key observation from these studies is that the facial selectivity of the reaction is directly correlated to the absolute configuration of the proline module of the ligand. For example, in comparing ligands **1a** and **1b**, which differ only in the configuration of the proline module, a considerable difference in enantiomeric ratio is observed for allylation of both aldehydes and ketones. Most notably, the allylation of benzaldehyde is promoted in nearly 90% *ee* (96:4 e.r. and 94.5:5.5 e.r.) using both ligands but with different senses of asymmetric induction. A similar effect is also found for the allylation of acetophenone. Systematic changes to the configuration of the other chiral centers in the ligand structure had only a subtle impact. These observations prompted us to explore the role of the proline module in greater detail.

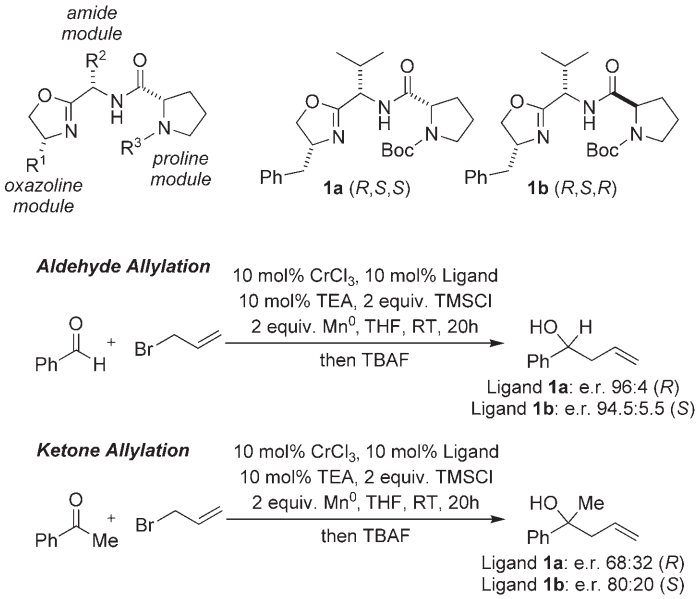

Figure 1. Effect of the proline module on facial selectivity in the Cr-catalyzed addition of allyl bromide to carbonyl compounds. Boc = *tert*-butyloxycarbonyl, TEA = triethylamine, TMS = trimethylsilyl, TBAF = tetrabutylammonium fluoride.

In order to initiate the investigation, we decided to make systematic changes to the proline module and probe the effect on the enantioselective outcome of the reaction. This was reasoned to be most easily accomplished through modification of the proline nitrogen, as proline carbamates can be either purchased from commercial sources or readily prepared by treatment of proline with the corresponding chloroformate.[10] Ligand **1a**, the optimal diastereomer for benzaldehyde allylation, was chosen as a starting structure to which carbamate modifications were made. Ligands **2a**–**2d** were synthesized from a common precursor,[10] by varying the size of the carbamate substituent from a small group (methyl)

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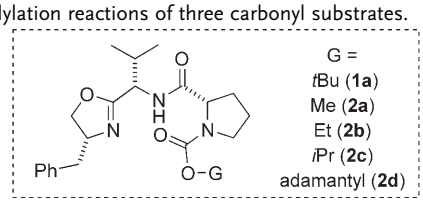
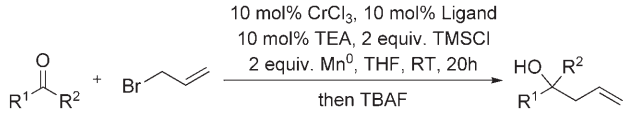
to a large group (adamantyl); the ligands were then initially evaluated for benzaldehyde allylation (Table 1). A trend between the relative size of the carbamate substituents and the enantiomeric ratio of the product was observed. The range is noteworthy (entries 1–5, Table 1) in that 20% *ee* (60:40 e.r.) is observed for the methyl substituent (entry 1) versus 92% *ee* (96:4 e.r.) for the 1-adamantyl substituent (entry 5); this corresponds to a difference of 1.62 kcal mol^{-1} at 25 °C in the diastereomeric transition states.

Table 1: Systematic evaluation of proline carbamate ligands in Nozaki–Hiyama–Kishi allylation reactions of three carbonyl substrates.





Entry	G	R^1	R^2	e.r. (R/S)[a]	Charton value (υ)[b]
1	Me	Ph	H	1.5	0.52
2	Et	Ph	H	1.9	0.56
3	*i*Pr	Ph	H	3.5	0.76
4	*t*Bu	Ph	H	23	1.24
5	1-adamantyl	Ph	H	23	1.33
6	Me	$PhCH_2CH_2$	H	1	0.52
7	Et	$PhCH_2CH_2$	H	1.1	0.56
8	*i*Pr	$PhCH_2CH_2$	H	1.3	0.76
9	*t*Bu	$PhCH_2CH_2$	H	2.8	1.24
10	1-adamantyl	$PhCH_2CH_2$	H	2.8	1.33
11	Me	Ph	Me	0.3	0.52
12	Et	Ph	Me	0.3	0.56
13	*i*Pr	Ph	Me	0.6	0.76
14	*t*Bu	Ph	Me	2.2	1.24
15	1-adamantyl	Ph	Me	2.6	1.33

[a] Enantiomeric ratio determined by HPLC equipped with a chiral stationary phase. [b] See reference [12a] for all Charton values except for 1-adamantyl.[12b]

Based on this initial success, we also evaluated two other substrates of interest: an aliphatic aldehyde, a particularly difficult substrate class for our current catalytic systems, and a simple ketone, acetophenone. Again, a correlation between the size of the group and the enantiomeric ratio is observed in both cases. A change in facial selectivity (e.r. < 1) is observed for acetophenone allylation (entries 11–15, Table 1) when going from smaller to larger G substituents. Notably, a similar magnitude of asymmetric induction for the catalyst containing the smallest group, **2a**, and the largest group, **2d**, is observed. This result highlights the capricious nature of the optimization process in asymmetric catalysis.

The most compelling aspect of these data is the ability to observe a linear free energy relationship by quantitatively correlating steric parameters to the log of enantiomeric ratio (a relative rate; Figure 2). To accomplish this, the steric parameters reported by Taft (based on ester hydrolysis rates)[11] and modified by Charton (based on van der Waals radii, plotted in Figure 2) were utilized.[12] Taft steric parameters have been commonly relied upon in the optimization of drug candidates.[13] Excellent correlations are observed for allylation of benzaldehyde, acetophenone, and the aliphatic aldehyde hydrocinnamaldehyde. The slope (ψ as defined by Charton) is a sensitivity factor much like a ρ value in a Hammett plot. The sensitivity is the greatest for benzaldehyde, but considerable for the other two substrates as well. Varying the size of the carbamate substituent could cause a number of structural changes, both subtle and global, in the diastereomeric transition states. However, the observation of linear free energy relationships is consistent with only one structural perturbation occurring upon modification of the carbamate. To the best of our knowledge, this is the first such reported correlation observed in asymmetric catalysis.[14]

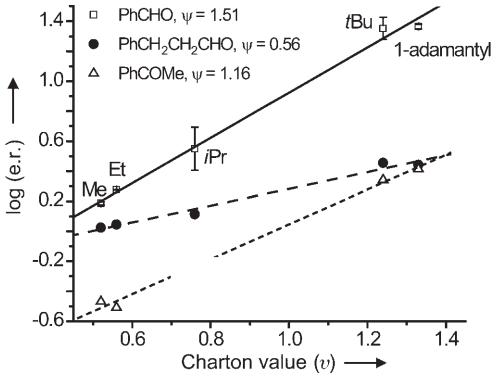


Figure 2. Three linear free energy relationships between Charton steric parameters and log of enantiomeric ratio (R/S).

Considering the volume of reported asymmetric catalytic reactions and variety of chiral ligands used, we were curious whether our current observation is unique. Perusal of the literature revealed several examples where a general trend was observed for the ligand-substituent size versus enantiomeric ratio. A noteworthy example was found by performing a similar analysis of the enantiomeric ratios from the seminal report by Pfaltz and von Matt concerning the use of phosphine oxazoline ligands in asymmetric Pd-catalyzed allylic alkylation reactions (Figure 3a).[15] We found that the size of the ligand substituent on the oxazoline can be correlated to product enantiomeric ratio with $\psi = 0.35$.[16] Another example, the enantioselective cyclopropanation of allylic alcohols with bis(sulfonamide)-derived chiral diamines and bis(halomethyl)zinc reagents reported by Denmark and co-workers, was analyzed (Figure 3b).[17] Again, a linear correlation in the Charton plot is observed. However, in this case, ψ is negative, consistent with a smaller ligand substituent leading to a higher enantiomeric ratio. This is in contrast to a paradigm in ligand design that bigger is better.

Correlating the size of the substrate to product enantiomeric ratio should also be possible, especially considering that the origin of Taft/Charton values is based on the effect of substituent size on the rate of ester hydrolysis.[11,12] As an example, the enantioselective aziridination of styrenes with Mn salen complexes reported by Komatsu et al. was analyzed (Figure 4).[18] In this case, the reaction of styrene results in a

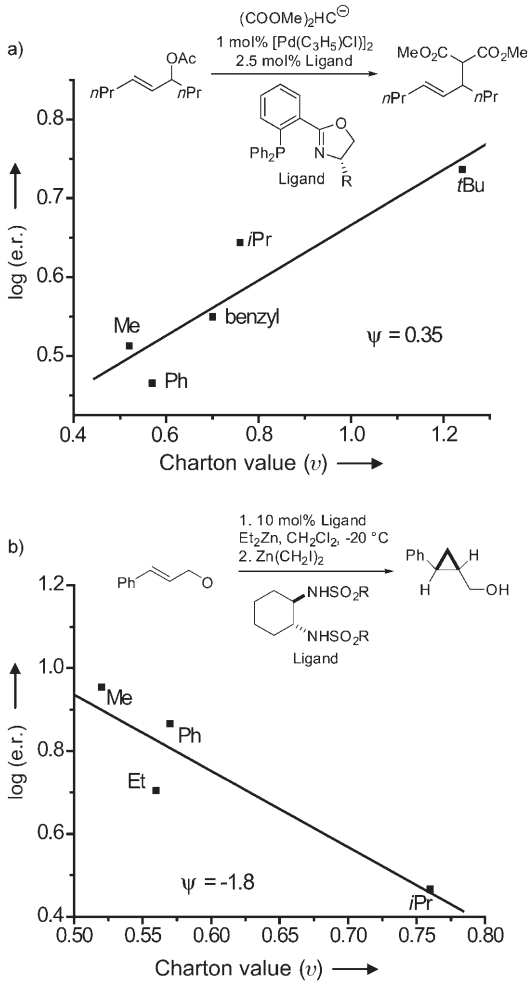


Figure 3. a) Charton plot of Pfaltz's enantioselective Pd-catalyzed allylic allylation using phosphine oxazoline ligands. b): Charton plot of Denmark's enantioselective cyclopropanation with bis(halomethyl)zinc reagents using bis(sulfonamide)-derived chiral diamines.

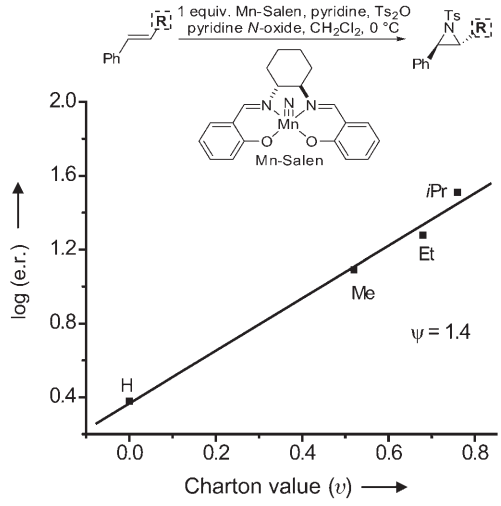


Figure 4. Charton plot of enantioselective alkene aziridination with Mn-salen reported by Komatsu et al.

significantly lower enantiomeric ratio than that resulting from substrates with substitution *trans* in the β position. An excellent correlation of the size of the group in the β position of the styrene is observed with $\psi = 1.4$.

We believe that the use of a Charton analysis should provide the opportunity to consider modifications to the ligand structure in a more predictable manner where it could become a useful tool for asymmetric catalyst optimization. Of particular note, the sensitivity factor ψ provides the practitioner with the ability to estimate the impact of making a change in substituent size and whether the synthetic endeavour may be worthwhile. For example, in our evaluation of hydrocinnamaldehyde, we found that the ψ value was relatively small and even significant changes to the size of the carbamate substituent are not anticipated to lead to high enantiomeric excess. This information is prompting us to think about other changes to the ligand design to obtain high enantioselectivity. Additionally, a Charton plot could provide insight into the transition state much like a Hammett plot. Specifically, the observation of a linear free energy relationship implies only a single structural change in the diastereomeric transition state is occurring by modification of the substituent.

In conclusion, we have reported the ability to construct linear free energy relationships of steric parameters and enantiomeric ratio for enantioselective carbonyl allylation reactions using modular oxazoline ligands developed within our laboratory. We have also extended this type of analysis to previously reported asymmetric reactions where substituent effects on the catalyst or the substrate can be correlated. Experiments to explore the origin of the Charton correlation in our system as well as others and exploitation of the linear free energy relationship in catalyst design are currently under investigation.

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