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Catalyst electronic polarizability and enantiomeric excess in asymmetric hydrogenation

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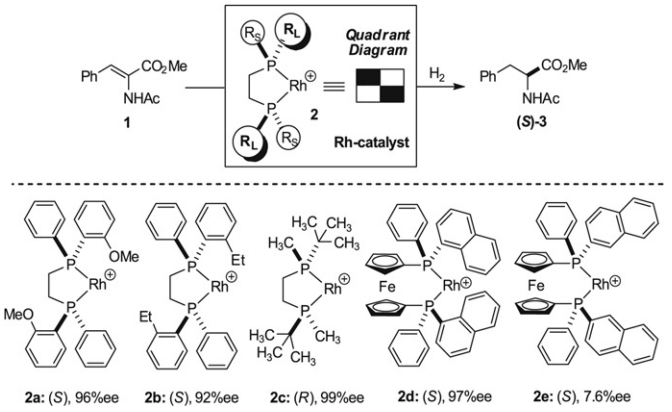
ABSTRACT

In the classical rhodium–diphosphine complexes-catalyzed asymmetric hydrogenation of enamide substrates, examination on the role of catalyst electronic polarizability in the origin of enantioselectivity reveals its linear free energy relationship with the product enantiomeric ratio that is much more pronounced than analogous correlation with steric effect in the same systems. From a conceptually novel scenario, this work suggests that the often-overlooked chiral catalyst local polarizability property may function as a controlling force in enantioselection thus has important implication in rational catalyst design.

1. Introduction

Asymmetric hydrogenation of dehydroamino acids catalyzed by diphosphine–Rh complexes represents a benchmark process of asymmetric catalysis, in which extensive reaction developments and mechanistic studies have yielded several classes of chiral catalysts capable of promoting high enantioselectivities.[1] For the origin of enantioselectivity in these reactions, the conventional wisdom usually holds that steric or geometrical properties of the relevant catalyst–substrate complex are the controlling factors, such wisdom culminates in a popular model termed quadrant diagram in explaining the spatial differentiation of a chiral catalyst toward its substrate thus the reaction stereochemical course.[2] Although the model is widely useful, outstanding exceptions had been noted by various authors.[3] Highlighted in Scheme 1 are five chiral catalysts[4] that promote asymmetric hydrogenation of (*Z*)-α-acetamidocinnamate **1** under identical or closely similar reaction conditions, and within the same Curtin–Hammett-type mechanistic framework.[5] All five catalysts can be geometrically characterized by the same quadrant diagram **2**, which in turn predicts that their predominant product enantiomer should be the same (*S*)-**3**. However, remarkably, catalyst **2c** induces a complete stereochemical reversal as compared to catalysts **2a**,**b**, leading to (*R*)-**3** in 99% ee; catalyst **2d** differs from **2e** only minimally in the position where the phosphorus atom attaches to the naphthalene ring. However, such a simple α-to-β switch was found to completely shut down the catalyst's ability to induce enantioselectivity. Moreover, with the so-called '*lock-and-key*' concept, another prevailing wisdom that describes the perfect geometrical



Scheme 1. Intriguing stereochemical observations in diphosphine–Rh complexes-catalyzed hydrogenation of **1**.

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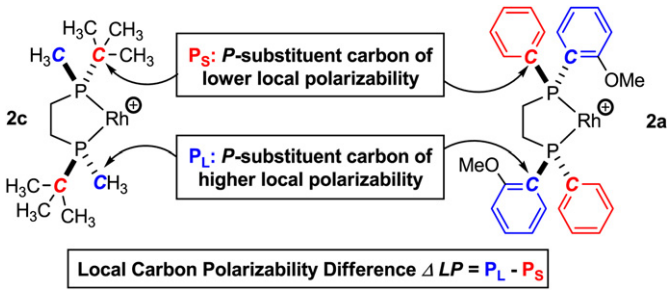
matching required for high enantioselectivity, it is generally difficult to rationalize why sterically distinctly different ligands (the keys), such as BINAP,[6a] DuPhos,[6b] Spiro-Phos,[6c] PhanePhos,[6d] Josi-Phos,[6e] FerroPhos,[4d] etc., could possibly achieve perfect fit with the same substrate **1** (the lock) and thus all deliver enantiomeric excesses greater than 99%. There is no doubt that enantioselectivity has roots in steric effects, but collectively these and other intriguing stereochemical observations compellingly invite consideration on a new scenario that might go beyond the conventional wisdom and might be more generally and predominantly responsible for the origin of enantioselectivity.

2. Results and discussion

One of us had published a new theory that concerns the importance of the role of electronic polarizability in molecular chirality and chiral interactions, particularly its implications in enantioselective catalysis.[7] Another author among us had extensively developed various computational methodologies correlating polarizability effects and philicity indexes with chemical reactivity and selectivity within the DFT framework, and also examined their utilities in a range of classical reactions.[8] Polarizability, as recently commented by Hansch,[9] the father of QSAR (Quantitative Structure–Activity Relationship) concept, is indeed a type of electronic effect that has long been overlooked by most computational chemists. The theory in essence is an extension of the classical hard and soft acid–base theory[10] into the dynamic three-dimensional chiral space.[7d] From a conceptually novel approach, it presented in great details how the analysis of a chiral catalyst's electronic polarizability property rationalized, generally and predictably, the stereochemical courses of many important asymmetric reactions reported since 1960s.[7a]

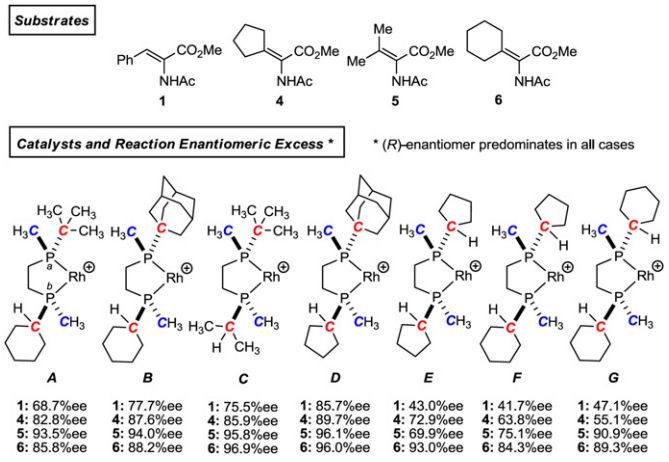
Application of this theory into the hydrogenation of **1** by catalysts **2a**–**e**, as disclosed earlier,[7a] reveals the local polarizability (*LP*)—but not the size—difference of the two P-substituents to be the predominant force leading to the observed enantioselections.[7a,b] Specifically, as shown in Scheme 2, the P-substituent of larger size in **2a** contains a carbon of higher local polarizability (P_L in blue),



Scheme 2. Inversed local electronic polarizability properties of the ligand *P*-substituent carbons in chiral catalysts **2a** and **2c**.

while in **2c** it has a carbon of lower local polarizability (P_S in red). The opposite P-substituents' local polarizability characteristics are responsible for the observed stereochemical reversal. In **2d**, the α-carbon atom of the naphthalene ring possesses a significantly higher polarizability than that of phenyl group thus ensuring high enantioselection, while in **2e** such a polarizability distinction is essentially absent. In these structures, we reasoned that computing the local polarizabilities of their corresponding P-substituent carbons and then plotting their polarizability differences $\Delta LP = P_L - P_S$ against the logarithm of the product enantiomeric ratio should quantitatively reveal linear free energy relationships.[11]

Fortunately, a range of structurally closely comparable C_2-symmetric or unsymmetric catalyst structures **A**–**G** had been systematically prepared by Imamoto and co-workers and also evaluated in Rh-catalyzed asymmetric hydrogenation of **1** and its related substituted enamide substrates **4**–**6** (Scheme 3), thus providing an ideal platform on which such a correlation may be readily tested.[12] It should be noted here that, as the origin of enantioselectivity is often complicated by many interplaying stereoeletronic factors, one could well envision that such a correlation derived exclusively from the predominant polarizability effects should be largely—but not perfectly—linear. It also merits a comment here that, although



Scheme 3. Structures of the substrates and the catalysts studied in asymmetric hydrogenation.

some inspirational computational work had been published aiming at rationalizing enantioselectivities in these and other related reactions,[13] our focus is conceptually different.

The catalyst backbone structures were optimized at B3LYP/6-31+G(d) level[14] of theory using the Gaussian 03W program.[15] Local polarizability LP is defined as (see Supplementary data for details):

$$LP = S^3 \times f_k^+$$

where S denotes the softness and f_k^+ is the Fukui function for the nucleophilic attack. The local carbon polarizability difference Δ*LP* at each of the two P-stereogenic centers can thus be calculated as:

$$\Delta LP = LP(\mathbf{C} \text{ of } CH_3) - LP(\mathbf{C} \text{ of } 2^o \text{ or } 3^o \text{ substitution})$$

Computational details and the ΔLP values at each of the two P-stereogenic centers (P_a and P_b as illustrated in catalyst ***A***, Scheme 3) in **A**–**G** are compiled in Supplementary data. The three plots of ΔLP (P_a), ΔLP (P_b), and ΔLP (P_a+P_b) against log(*R*/*S*) on each of the four enamide substrates are shown in Figure 1. The first two plots are particularly informative as they correlate the polarizability differences at each individual phosphorus center directly to the magnitudes of enantioselectivities. It is transparent that, although with a few outliers (constantly associated with structure **C** and to a lesser extent, structure **A**), a good linear relationship was uncovered in each case, highlighting the inherent correlation between the catalyst local polarizability properties and enantiomeric excesses.

Since these chiral phosphines were synthesized with well-established methods in essentially enantio-pure forms (>99% ee) and reaction enantioselectivities were evaluated by chiral HPLC analysis with high accuracy, the perturbations on correlation linearity from experimental errors associated with the enantio-purities

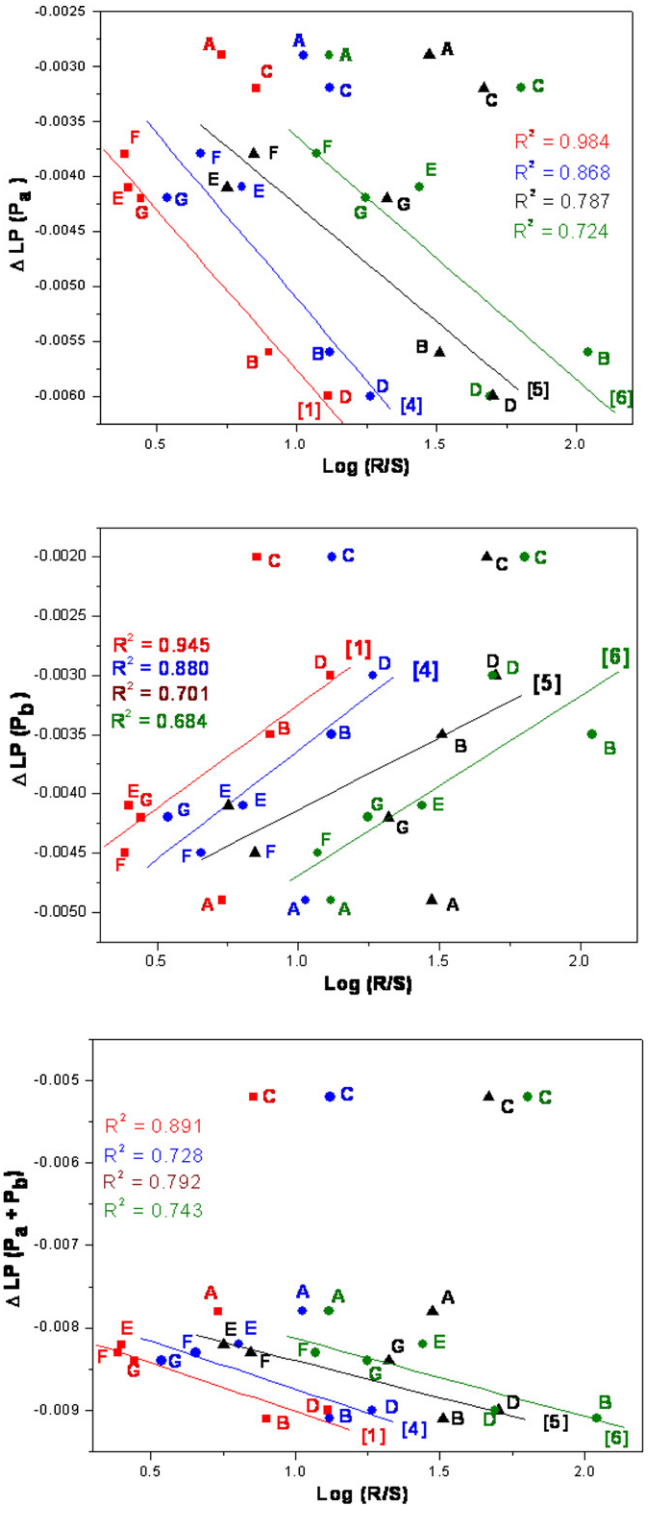


Figure 1. Linear free energy relationships between catalyst local carbon polarizability difference ΔLP (P_a), ΔLP (P_b), ΔLP (P_a+P_b) and log(*R*/*S*) in asymmetric hydrogenation of enamides **1** and **4**–**6**.

of certain diphosphine ligands and reaction products were expected to be minimal. We therefore envisioned that the deviations from perfect linearity and occurrences of outliers of ***A*** and ***C*** are most likely resulted from steric or conformational factors on the experimentally defined reaction enantioselectivities. To quantitatively evaluate the influence of steric effects on reaction enantioselectivities, following Sigman and co-workers' latest proposal,[11,16] the Charton steric volumes[17] of the P-substituents were employed and the steric difference Δ*S* at each of the two P-stereogenic centers was plotted against log(*R*/*S*) for the four substrates. The results were summarized in Figure 2. The plots of Δ*S* versus log(*R*/*S*) at P_a positions

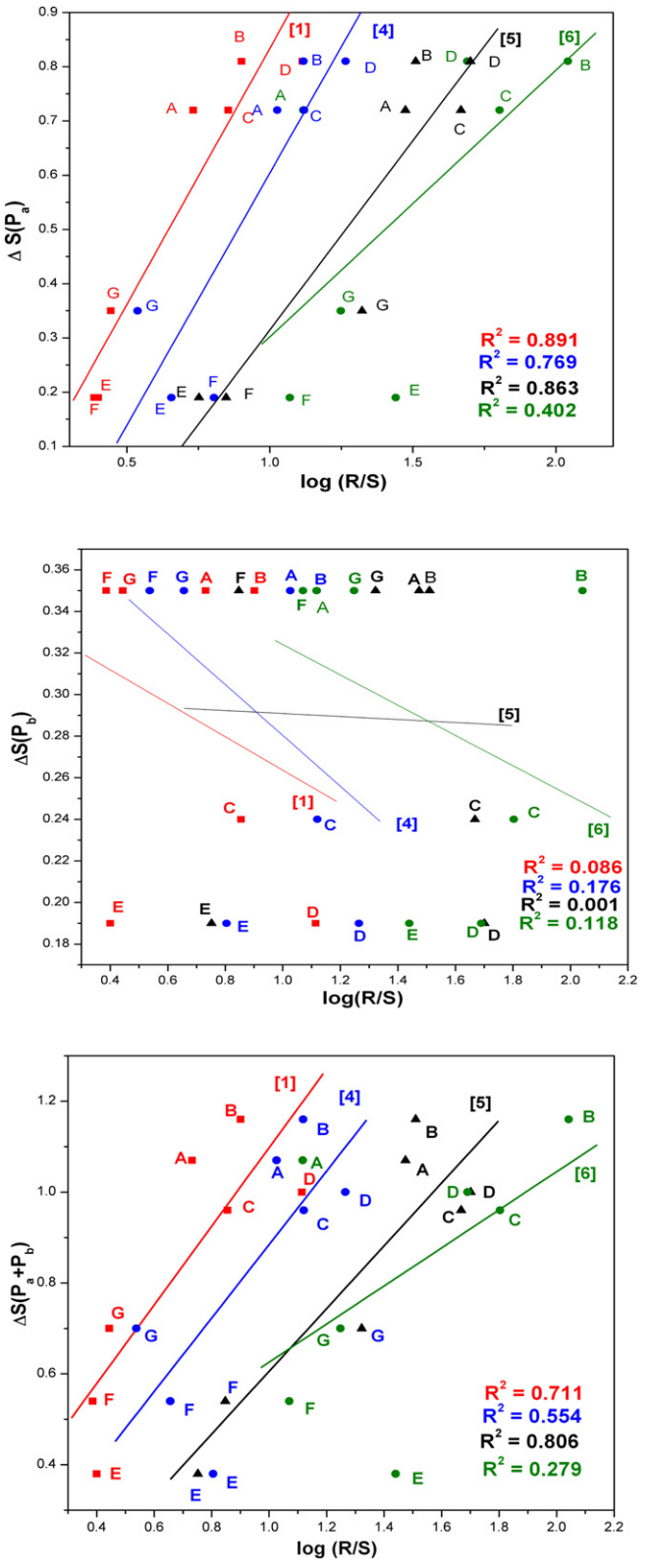


Figure 2. Correlations between catalyst P-substituents' steric size (Charton values) difference Δ*S* (P_a), Δ*S* (P_b), Δ*S* (P_a+P_b) and log(*R*/*S*) in asymmetric hydrogenation of enamides **1** and **4**–**6**.

appeared to be more coherent than those at P_b positions, implying the larger steric differences at P_a positions do indeed impose more significant influences on the reaction enantioselectivities. But in general, those correlations show much worse fittings and are poorly linear as compared to those summarized in Figure 1. The nonlinear dependence observed seemed to suggest that enantioselectivities are more sensitive to the tertiary or secondary P-substitution patterns rather than the substituents' individual steric volume. These comparisons on polarizability and steric effects in the same contexts further highlight predominant electronic control in the origin of enantioselectivities in these reactions, and the occurrences of outliers associated with two of the most crowded catalysts (***A*** and ***C***) suggest that steric influences become significant only when the P-substituents' sizes accumulate to extreme bulkiness.

In order to check the relative importance of both the steric and the polarizability effects on enantioselections, we presented in Supplementary data (see Tables 6–9 and Figs. 8–11 therein) the related two-parameter regression models. In most cases the correlations were improved considerably when compared with the corresponding one-parameter models and moreover, there was hardly any outlier. These results confirmed that although both polarizability and steric size can be important, the former evidently generally weighs more significantly than the latter in controlling enantioselection.

3. Conclusion

In summary, the role of electronic polarizabiltiy in the origin of enantioselectivity in the chiral diphosphine–Rh complexes-catalyzed asymmetric hydrogenation of substituted enamides was investigated. The observed linear free energy relationship correlations between various catalysts' local substituent polarizability difference and the logarithm of the experimental product enantiomeric ratios highlighted the significance of the often-overlooked polarizability effect in asymmetric induction. Consideration on these new types of electronic factors, in conjunction with conventional steric theories, should aid rational catalyst design and discovery under a conceptually new scenario. Our continuing efforts along this thematic line will be reported in due course.

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Supplementary data

Computational details and individual free energy relationship plot on each of the enamide substrates examined. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.055. This data include MOL files and InChIKeys of the most important compounds described in this article.

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