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Steric Effect of Protonated Tertiary Amine in Primary−Tertiary Diamine Catalysis: A Double-Layered Sterimol Model

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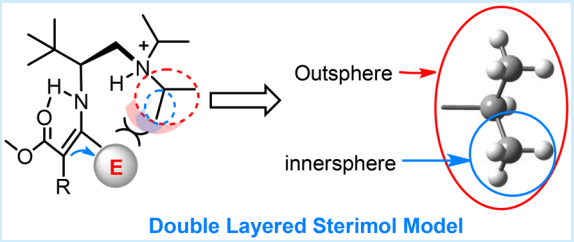
Supporting Information

ABSTRACT: Steric shielding effects are seldom adopted in the stereocontrol with chiral primary amine catalysts. An unexpected steric shielding effect of protonated tertiary amine, a typical hydrogen-bonding moiety, was disclosed. A linear free energy relationship between structure and enantioselectivity was established in three reactions when a double-layered Sterimol model was introduced.



Pursuing exquisite stereocontrol is one of the ultimate tasks in asymmetric catalysis. However, the search for an optimal catalyst still relies on the evaluation of a considerable number of catalyst structures, and rational design of chiral catalysts remains a great challenge. Therefore, understanding the relationship between enantioselectivity and catalysts structures is urgently desired but still underdeveloped. The challenge mainly comes from the small activation energy difference between two transition states corresponding to two enantiomers, wherein a 2.7 kcal/mol disparity would give an excellent enantioselectivity, >98% ee.[1] Efforts in this trend by using classical physical organic methods, especially linear free energy relationship analysis, have been proven to be powerful strategies to understand the intrinsic origin of enantiocontrol and enable predictive catalyst design.[2] Initial studies along this line mainly focused on the evaluation of electrostatic characters of the catalysts, including Hammett σ parameters,[3] pK_a,[4] polarizability,[5] etc. However, research of the relationship between steric effects and enantioselectivity has only emerged in the past decade. Since 2008, Sigman and co-workers have reported a series of studies on the relationship between steric effects and the reaction chiral outcome.[6] Various steric parameters have been used to elucidate the structure−enantioselectivity relationships, including Charton steric parameter[6a,b] and Winstein−Holness parameter (A value) interference values[1] as well as the Sterimol parameter.[6d] Meanwhile, stepwise regression analysis was also introduced to deal with the multidimensional parameters. Further successes were obtained when combined parameters were used in the correlation with the same technique.[7] Along these lines, IR vibrations, bond lengths, bond angle, atom charges, NMR shifts, and so on were all selectable parameters, and meaningful information can be drawn from the analysis of the reaction mechanisms as well as the origin of enantiocontrol.[8]

The past decade witnessed the blossom of chiral primary−tertiary diamine catalysts, which showed powerful capabilities in the enantioselective transformation of carbonyl compounds,[9] especially for the more hindered ketone substrates.[10] It was found that the hydrogen-bonding effects were mainly adopted for those privileged catalysts in order to achieve stereocontrol.[11] Recently, we observed an unusual steric effect caused by the protonated tertiary amine moiety in Robinson annulations,[12] where an dual activation mode was found in this catalytic process. Later on, a much more obvious steric effect was observed in the primary amine/palladium-cocatalyzed asymmetric allylic alkylation (AAA) reactions.[13] Detailed studies showed that a novel linear free energy relationship could be drawn when a double-layered Sterimol model were introduced. The model could also be applied to two other reactions (Figure 1).

In the chiral primary amine/Pd-catalyzed AAA reation,[13] bulky primary **3i** was identified as the optimal catalyst (Scheme 1). Surprisingly, the absolute configuration of the newly formed all-carbon quartnery stereocenter was determined as S, which could not be explained by the normally occurring H-bonding model with protonated tertiary amines (Figure 1). A

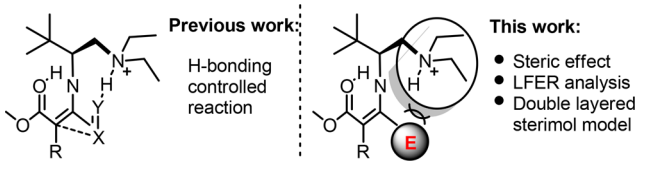


Figure 1. Enantiocontrol with our catalysts.

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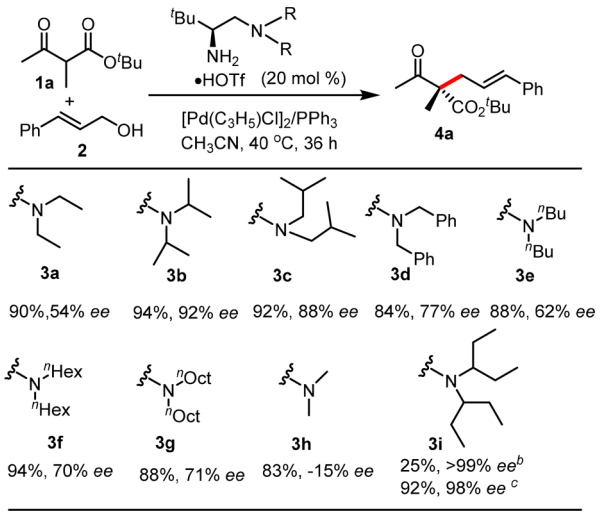
Scheme 1. Catalyst Screening for the Allylic Alkylation[a]



[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.10 mmol), chiral amine (20 mol %), Pd precursor (5 mol %), PPh_3 (20 mol %), CH_3CN (0.5 mL), 40 °C, 36 h. [b]Reaction time: 40 h. [c]The reaction was carried out with 3 equiv of ketoester **1a**, and the reaction time was extended to 72 h.

Si-facial attack transition-state model was thus proposed to account for the observed stereoselectivity. In this model, steric effects played a key role in channeling the attack of π-allyl palladium species, for which a notable H-bonding site is lacking. The observed bulky substituent effects of the tertiary amino moiety are clearly in support of this steric model.

In order to elucidate the steric effects of the tertiary amine moiety, we have tried to determine the linear free energy relationship between structure and enantioselectivity. As one type of widely used steric parameters, the Charton values were evaluated first to account for the observed enantioselectivity; however, the variance was found to be only 0.57, and no obvious linear relationships could be drawn (Figure 2A). In

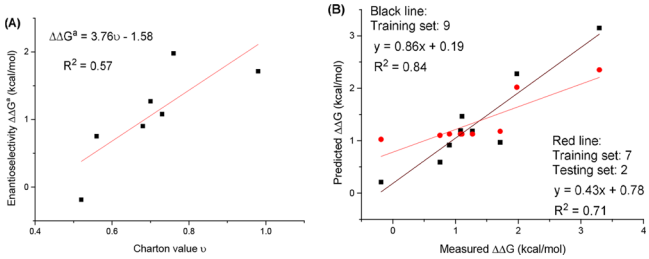


Figure 2. Charton (A) and sterimol (B) plot with our catalysts.

view of the huge successes of Sterimol parameter-based simulation in asymmetric catalysis, we further tried the multivariate linear least-squares regression analysis using the three-dimensional Sterimol parameters, and a better result was obtained with R^2 = 0.84 (Figure 2B). It was found that the minimum width of the substituent played a critical role in this model, with a large coefficient of 4.67 (eq 1). However, when we reduced the training set to seven samples and these catalytic results with **3h** and **3i** were treated as testing sets, even worse results were obtained with R^2 = 0.71 (Figure 2B). The predicted $\Delta\Delta G^a$ for the testing sets are much different from the measured results (eq 2), indicating this model was unworkable for an efficient prediction.

$$\Delta\Delta G^a = 4.67B_1 + 0.21B_5 - 8.19 \quad (1)$$

$$\Delta\Delta G^a = 2.55B_1 - 3.31 \quad (2)$$

The failure mentioned above indicated neither Charton nor Sterimol parameters were sufficient to describe the nature of the substituents. Further analysis showed that the inner fine structure of the substituents was also important for the stereocontrol; therefore, an additional structure descriptor was necessary to characterize the nature of the inner structures. Considering this, we developed a double layered Sterimol (DLS) model in which the innersphere was described by an additional suite of Sterimol parameters (Figure 3). Multivariate

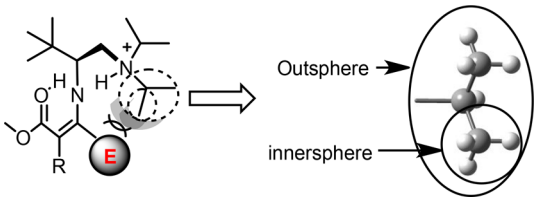


Figure 3. Double-layered sterimol model.

linear least-squares regression analysis with the DLS model produced an equation shown as eq 3. The equation includes three statistically significant terms, the minimum width parameter of the outsphere (B_1), the minimum width parameter of the innersphere (B_1'), and the offset. The coefficient of these terms indicated that both of the minimum widths of outspheres and innerspheres showed significant influence on the enantioselectivity, and the predicted $\Delta\Delta G^a$ showed good correlation with the experimental results, with an R^2 = 0.94 (Figure 4). Leave-one-out cross-validation

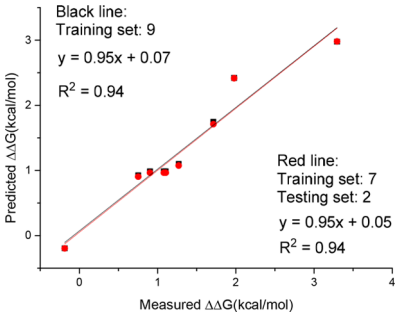


Figure 4. Double-layered sterimol model and correlation between computational and experimental results.

(LOOCV) was implemented to test the predictive performance of this model, and the Q^2 was found to be 0.83, indicating this model is acceptable[14] (see Table S7). We also tried to omit two pieces of data from the training set and listed them as the testing set to evaluate the prediction ability; in this case, the data with catalysts **3d** and **3e** were selected as testing data as their catalytic outcomes were moderate. Again, a similar satisfactory correlation was found (eq 4), and the prediction was accurate. Omitting the boundary data such as **3h** and **3i** also gave a satisfied correlation, and the predicted results with **3h** and **3i** were in accordance with the experimental observations (see Figure S3).

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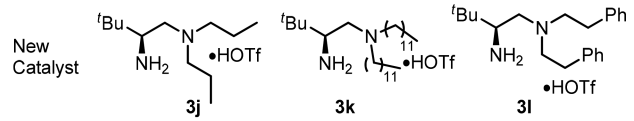
$$\Delta\Delta G^{a} = 4.15B_1 + 1.88B_1' - 9.45 \quad (3)$$

$$\Delta\Delta G^{a} = 4.20B_1 + 1.84B_1' - 9.49 \quad (4)$$

With this model in hand, we further predicted the performance of several new catalysts which were not evaluated before.[15] As can be seen in Scheme 2, the predicted $\Delta\Delta G^{a}$ were similar to the observed ones, with a maximum deviation of 0.17 kcal/mol; these studies further verified the predictive power of this model. We then resimulated the equation with the whole data set; similar results were obtained as shown in eq 5.

Scheme 2. New Catalyst Testing for the Allylic Alkylation



	3j	3k	3l
Predicted $\Delta\Delta G^{a}$	0.99	1.03	0.99
Predicted *ee*	66%	68%	66%
Observed $\Delta\Delta G^{a}$	1.13	0.99	1.16
Yield and *ee*	84%, 72% *ee*	78%, 66% *ee*	87%, 73% *ee*

$$\Delta\Delta G^{a} = 4.08 + 1.89B_1' - 9.33 \ (R^2 = 0.94) \quad (5)$$

Why did the minimum width of the innersphere show such a significant influence on the enantioselective outcome? The reason could be found in the conformation of the *N*-substituents. We have mapped the conformations of the flexible *N*-substituents of enamine **3a** and enamine **3b** with molecular dynamic methods,[16] and the four conformers with lowest energy of each catalyst were further optimized with DFT calculations; the most stable conformations are shown in Figure 5. The orientation of the terminal methyl group was found to be on the enamine side, thus making a large contribution to the steric shielding on the *Re* face. We have successfully characterized the enamine structure of **3a** by X-ray analysis, and the configuration of the *N*-substituent was exactly the same with our computational results. Further enlarging the substituent could give more shielding capability, and the observed increasing trend in enantioselectivity agreed with this model.

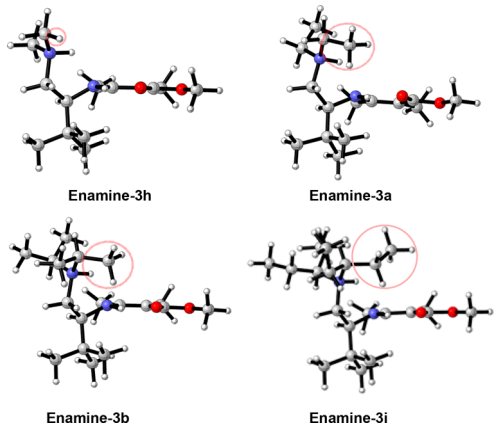


Figure 5. Orientation of the N-substituent in the enamine intermediate.

In order to test the validity of this model, we further tested the pyrrolidine- and piperidine-type primary amine catalyst **3m** and **3n**. Due to the cyclic structure, the orientation of the larger group on C1 was not directly toward the *Re*-face; thus, the space-shielding effect should be much smaller than that for the *N*-ethyl-substituted catalyst (Figure 6). The experimental studies showed that catalyst **3m** gave similar results with the *N*-methyl-substituted catalyst **3h** (5% ee with *R*-configuration); as for **3n**, only 25% ee with *S*-configuration was obtained, which is much smaller than that of **3a** (Scheme 3).

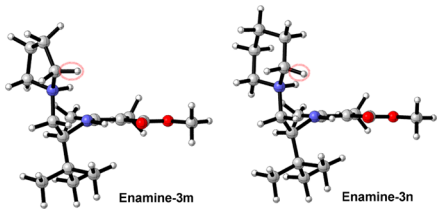
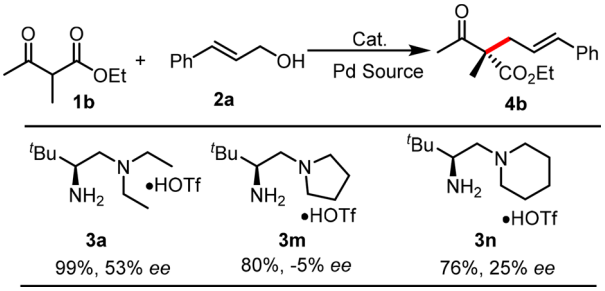


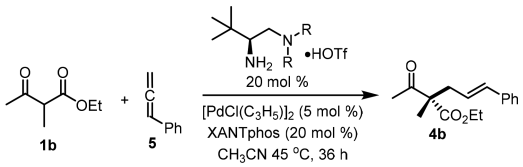
Figure 6. Steric shielding of enamine with catalysts **3m** and **3n**.

Scheme 3. Catalytic Performance of 3m and 3n

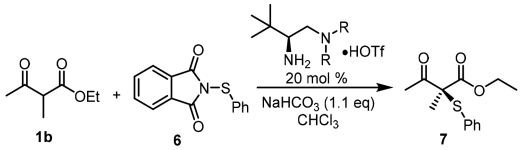


We have also realized the enantioselective terminal addition of carbonyl compounds to allenes by synergistic incorporation of primary amines and palladium catalysts in 2017.[17] Similar allylic alkylation products could be generated which were far beyond the reach of the reactions with allylic alcohols. A similar steric effect was found in this system, and multivariate regression analysis with the **DLS** model gave a good correlation with a R^2 = 0.89. The produced equation is presented in eq 6. Again, the outsphere B_1 and innersphere B_1' showed significant influence on the enantioselectivity (Scheme 4, eq 6, and Figure S4A). Besides the allylation reactions, such steric effects could also be found in other important

Scheme 4. Primary Amine Catalyzed Allylic Alkylation and Sulfuration Reaction



$$\Delta\Delta G^{\ddagger} = 1.30B_1 + 1.60B_1' - 4.37 \quad \text{(eq 6)}$$



$$\Delta\Delta G^{\ddagger} = 1.76B_1 + 1.75B_1' - 4.97 \quad \text{(eq 7)}$$

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transformations. Recently, we developed the chiral primary−tertiary diamine catalyzed sulfuration reaction of ketones.[18] Survey of the catalysts showed significant dependence on the size of the *N*-substituents (see the SI). Regression analysis also showed that the enantiocontrol was mainly determined by the outsphere *B*1 and innersphere B_1' (Scheme 4, eq 7, and Figure S4B). These findings further confirmed the applicability of this DLS model.

In conclusion, we have developed a double-layered Sterimol model to account for the steric effect on enantioselectivity in the dual primary amine/palladium-catalyzed asymmetric allylic alkylation reactions. The results showed that both the minimum width of the outsphere (B_1) and the innersphere (B_1') had a big influence on the enantio-outcome. Further analysis showed the origin of this steric shielding effect comes from the proper orientation of the *N*-substituents during the catalytic process. This model was also effective in several other primary amine-catalyzed reactions where H-bonding was absent, indicating the influence of the *N*-substituent orientation was general in primary amine-based catalysis. This finding gave us useful hints toward the development of new primary amine catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03584.

Experimental procedures, screening data, steric parameters and model development, computational details, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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