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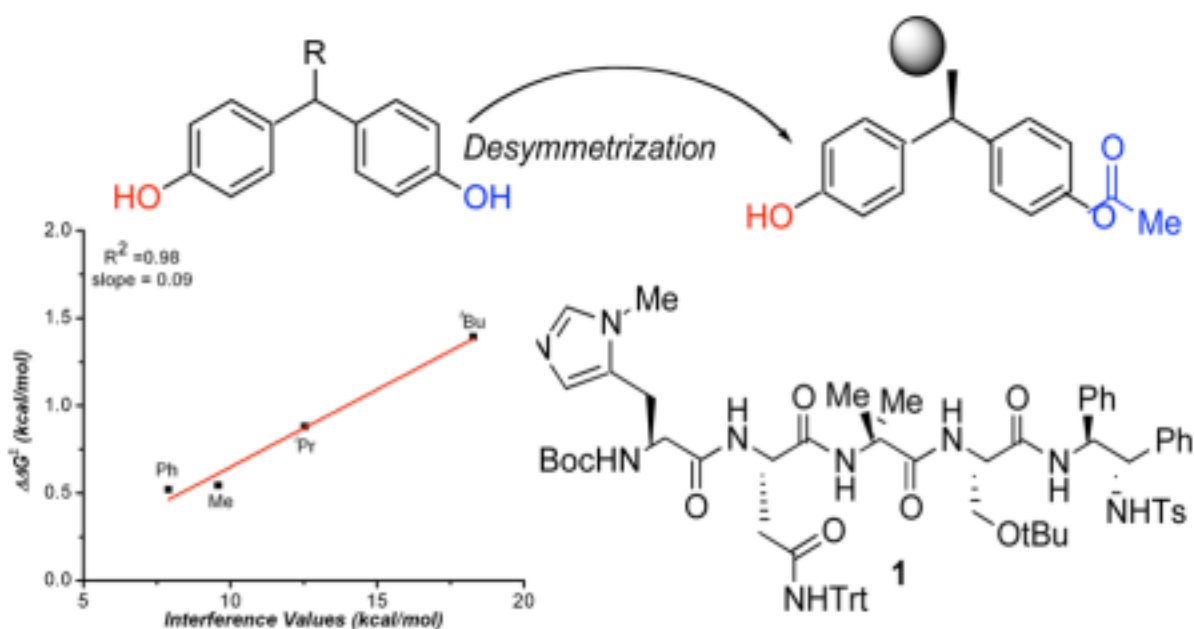
## Linear Free Energy Relationship Analysis of a Catalytic Desymmetrization Reaction of a Diarylmethane-Bis(phenol)

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### Abstract



Linear free energy relationships have been found for enantioselectivity and various steric parameters in an enantioselective desymmetrization of symmetrical (bis)phenol substrates. The potential origin of this observation and the role of different steric parameters are discussed.

The analysis of enantioselectivity in catalytic reactions is a highly challenging endeavor due to the small differences in absolute energies of competing transition states that lead to useful levels of selectivity. In the case of enantioselective reactions, a mere 2.7 kcal/mol of partitioning between competing transition states can lead to the gold standard of success in the field, >98% ee. As a result, catalyst design from first principles remains a daunting task, leading to a substantial reliance on empiricism.<sup>1</sup> Moreover, after-the-fact analysis of the basis of observed selectivities remains highly challenging in and of itself. As a result, tools that assist in quantitative analysis of reaction outcomes are of great value. In fact, correlation techniques, perhaps best exemplified by the venerable Hammett analysis,<sup>2</sup> are now entrenched methods

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that ground organic chemistry as a quantitative science.<sup>3</sup> The development of quantitative tools for the analysis of catalytic enantioselective reactions has evolved more slowly than for other types of reaction analysis. In part, this may be due to the often mechanistically complicated reaction coordinates that characterize catalytic enantioselective reactions. In any case, Sigman *et al.* recently demonstrated a series of quantitative studies of enantioselective processes employing linear free energy analysis.<sup>4</sup> This analysis is aimed at both gaining further insight into the origin of steric effects but also to help develop predictive power in the design of new catalysts.

Recently, Lewis *et al.* demonstrated that peptide catalyst **1** is able to efficiently catalyze the desymmetrization of symmetrical (bis)phenol **2** (Scheme 1), which bears a bulky *t*-Bu group at the prostereogenic center (80% yield, 97.5:2.5 er).<sup>5</sup> Given the unusual nature of this reaction, and the curious role of the remote prostereogenic center, we sought to study this reaction further. Indeed, we set out to probe the role of steric bulk at the key position through the synthesis of a series of (bis)phenols with a varying degree of steric bulk at the prostereogenic center.<sup>6</sup> Whereas the *t*-Bu-bearing compound **2** was converted to the monoacetate with 97.5:2.5 er, the *i*-Pr-bearing compound **3** was converted to its mono acetate with 86.5:13.5 er. The Et-substituted compound **4** delivered its derived product with 78.5:21.5 er, and finally the Me-bearing compound **5** gave the product with a lower, but perhaps still remarkable 76.0:24.0 er. In fact, we were quite surprised by the seemingly well-behaved trend for this remote steric effect, and we wished to understand it in a quantitative way. For this goal, we turned to the linear free energy analysis of catalytic enantioselective reactions of Sigman,<sup>7</sup> and the striking results are presented herein.

One of the challenges associated with this study was the identification of appropriate reference parameters for the linear free energy relationship analysis. As shown in Figure 1, one might imagine exploitation of Charton values (Figure 1a), Winstein-Holness values (“A-values,” Figure 1b), or Interference values (Figure 1c), *inter alia*, to the analysis. Charton values ( $\nu$ ),<sup>8</sup> which are based on the Taft steric parameters (Figure 1a)<sup>9</sup> with modifications to take inductive and resonance factors into account, are perhaps the most studied and well-developed steric parameter.<sup>10</sup> With this in mind we wished to expand upon the initial set of bis(phenols) to include a diverse array of substrates containing substituents for which reported  $\nu$  values were available.

As shown in Table 1, we found that the substrates in which the steric bulk was located at the carbon  $\alpha$  to the prostereogenic center (entries 1–7) exhibited a strong correlation between enantioselectivity (plotted as  $\Delta\Delta G^\ddagger$  which is derived from enantiomeric ratio) and  $\nu$  (Figure 2). The large slope ( $\psi$ ) for this plot ( $\psi = 1.39$ ) indicates a strong sensitivity to changes in sterics at the prostereogenic center. This may suggest that the substitution at the  $\alpha$  carbon leads to a propeller-like twist between the aryl rings of **2**, where decreased steric bulk causes a less rigid system with a lower barrier to interconversion between the two possible propeller twists. This in turn could make diastereotopic recognition by the catalyst more difficult. Another possible explanation is that since peptide **1** was optimized specifically for (bis)phenol **2** through several directed libraries, the alkyl group steric bulk at that position might be needed for some sort of substrate-catalyst interaction.

Interestingly, this correlation seems to break down for substrates in which the steric bulk is further removed from the prostereogenic center (Figure 2). This may be related to entropic effects, associated with the ability of the bonds in the substrate to rotate in such a way as to minimize steric contacts between the alkyl substitution and the phenol rings, causing the bulky substituent to behave more like a smaller ethyl group than a *t*-Bu group, similar to what is seen in cyclohexanes (Figure 3a). In the context of hydrolysis of an ester, steric bulk at the  $\beta$  position will still significantly hinder the  $\pi^*$  orbital (Figure 3b) of the carbonyl resulting in a large  $\nu$ .

Thus for these substitutions, Charton values may indicate a steric effect greater than what may actually be present.

With that in mind, we decided to investigate whether other steric parameters may provide a more appropriate correlation. Winstein-Holness values (A-values)<sup>11</sup> may well be the most commonly quoted steric parameter. They are derived from the energy difference between the equatorial and axial conformers of mono-substituted cyclohexanes.<sup>12</sup> A-values are commonly used as a teaching tool to first introduce conformational analysis and the concept of steric bulk (Figure 1b). We thus wondered if A-values might be better suited to our system due to the sensitivity of A-values to gauche-type torsional strain (Figure 4a). For example the A-values of *t*-Bu and CH<sub>2</sub>*t*-Bu are 4.5 kcal/mol, and 2.0 kcal/mol, compared to Charton values where  $\nu = 1.24$ , and 1.34 respectively.

Indeed, a strong correlation between  $\Delta\Delta G^\ddagger$  and A-values was observed (Figure 4). Unfortunately, to our knowledge, the breadth of A-values available in the literature is not near that of Charton values, making it difficult to make a complete comparison. For example, in Figure 4, if one were to exclude the *tert*-butyl group, the quality of the correlation would suffer. Yet, the inclusion of R-groups such as adamantyl would likely improve the correlation, were the additional and appropriate parameters available. Nonetheless the correlation between  $\Delta\Delta G^\ddagger$  and A-values is encouraging and we believe, based on analysis of hand held models, this trend would hold for the substrates in which there are no reported A-values.

Since the early part of the 20<sup>th</sup> century chemists have been qualitatively describing steric bulk from data derived by observing the  $t_{1/2}$  of racemization of ortho, ortho' substituted biaryls.<sup>13</sup> Since the bis(phenol) structure **1** bears both aryl moieties, as well as substituents residing on an sp<sup>3</sup>-carbon center, we wondered if interference values might also provide an insightful correlation parameter. This question was facilitated by the explicit studies of Sternhell and coworkers, who applied modern NMR techniques, and a well-designed molecular system (Figure 1c) to quantify these trends in the form of interference values ( $I^{X-H}$ ).<sup>14</sup> Though interference values are very limited in number in the literature, we made a preliminary plot which demonstrates an excellent correlation between enantioselectivity and  $I^{X-H}$  (Figure 5).

In summary, we have successfully constructed linear free energy relationships for a unique enantioselective desymmetrization of bis(phenol) substrates containing a remote stereocenter. To accomplish this, three distinct steric parameters including Charton values, A-Values, and interference values were correlated to the enantiomeric ratio of the desymmetrization reaction. While precise catalyst/substrate information must be interpreted carefully, an important conclusion is that one must understand the origin of the parameter being investigated. Specifically, we found success using Charton values for substrates with the steric bulk directly adjacent to the chiral center; however, when the steric bulk was distal to the chiral center, a poor correlation resulted. In contrast, better correlations with A-values and interference values were found although only a limited set of values is currently available. This work clearly illustrates the usefulness of steric parameters in asymmetric catalyst analysis but also highlights the caution one must use in evaluating steric effects as well as the need to develop new or more complete sets of steric parameters.

## Supplementary Material

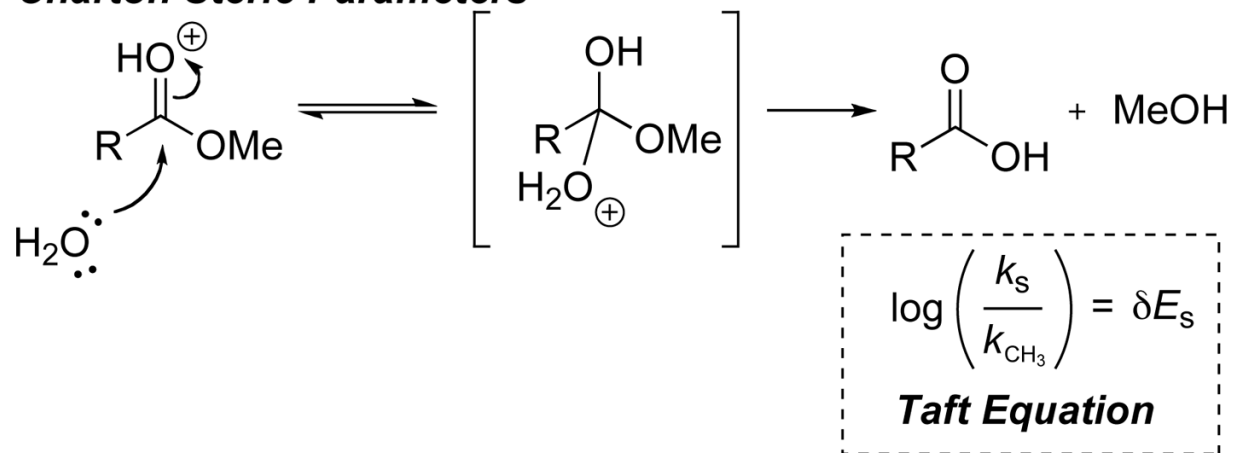
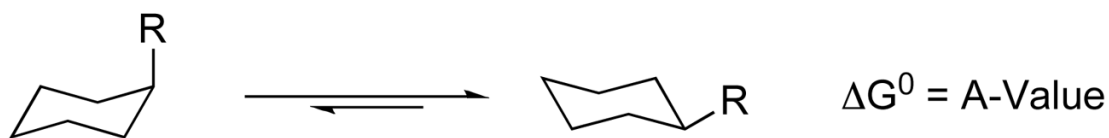
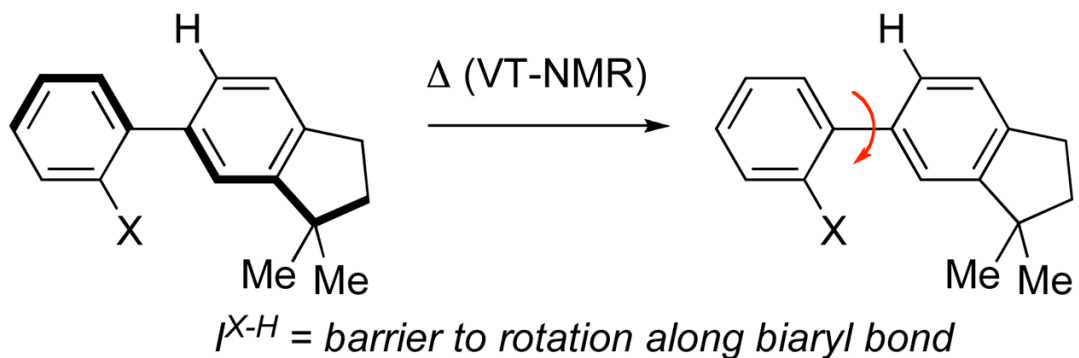
Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

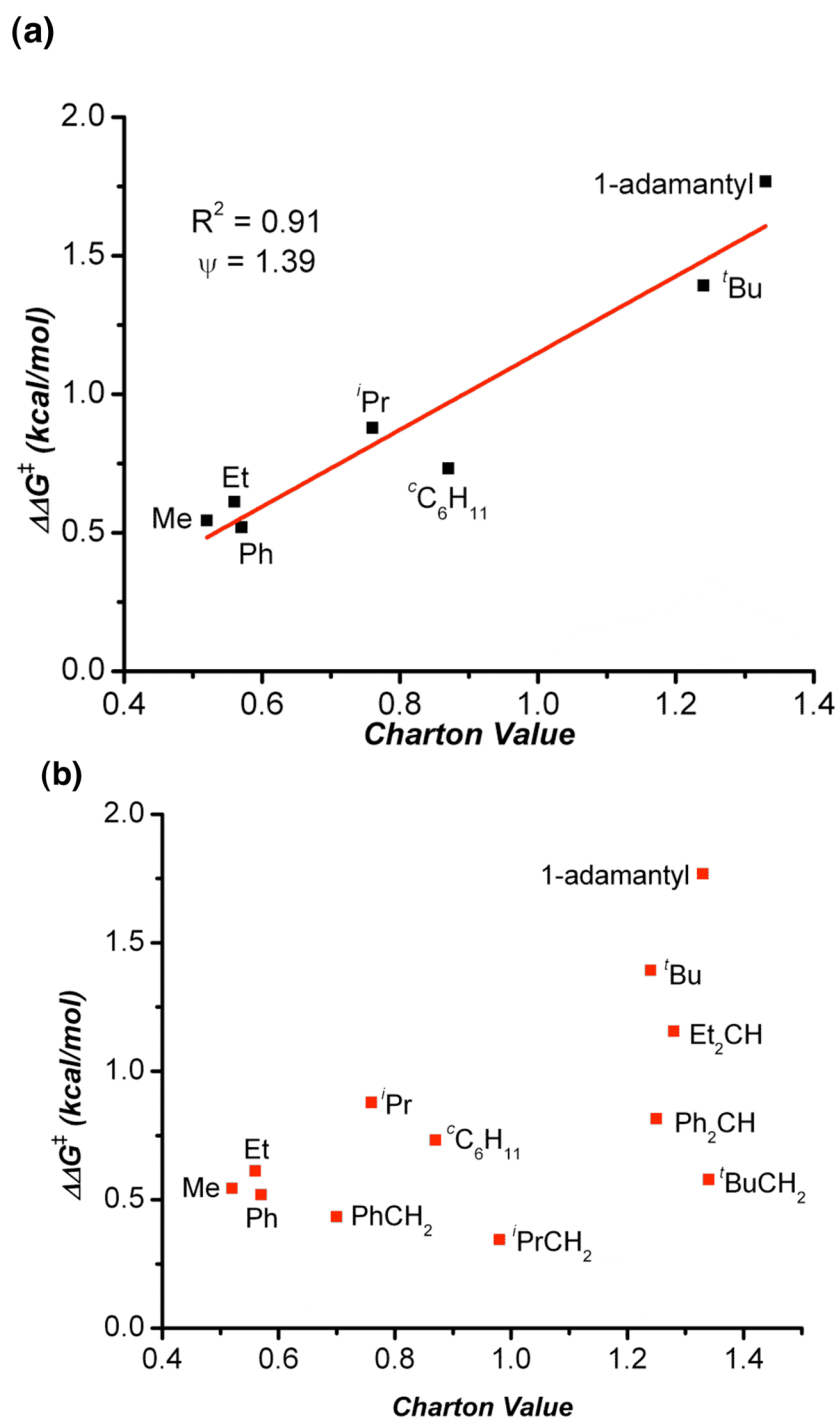
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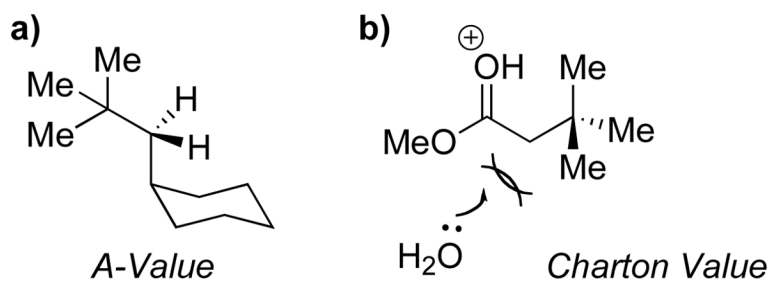
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**(a) Charton Steric Parameters****(b) Winstein-Holness Parameters (A-Value)****(c) Interference Values**

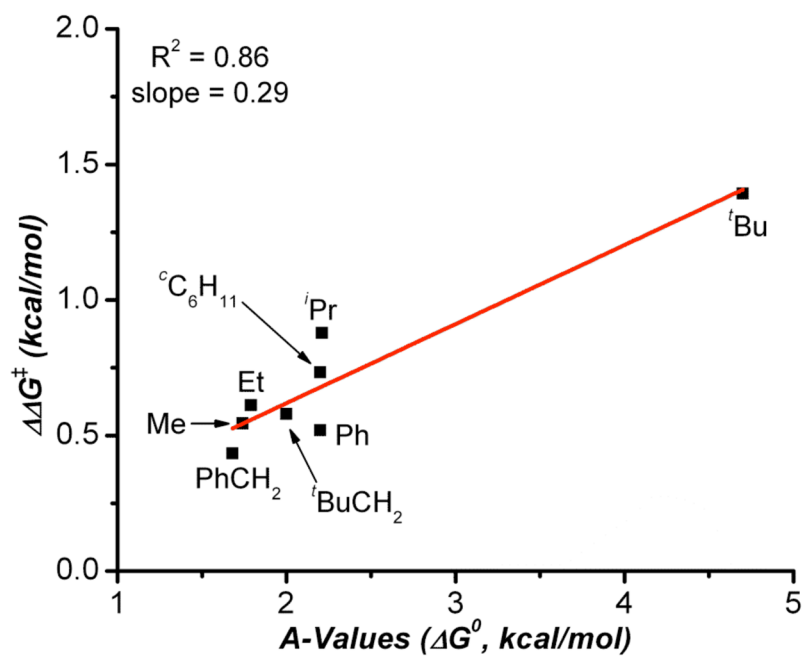
**Figure 1.**  
Origin of common steric parameters.



**Figure 2.** (a): Charton plot of selected substituents with bulk  $\alpha$  to the prostereogenic center. (b): Charton plot of all substituents evaluated.

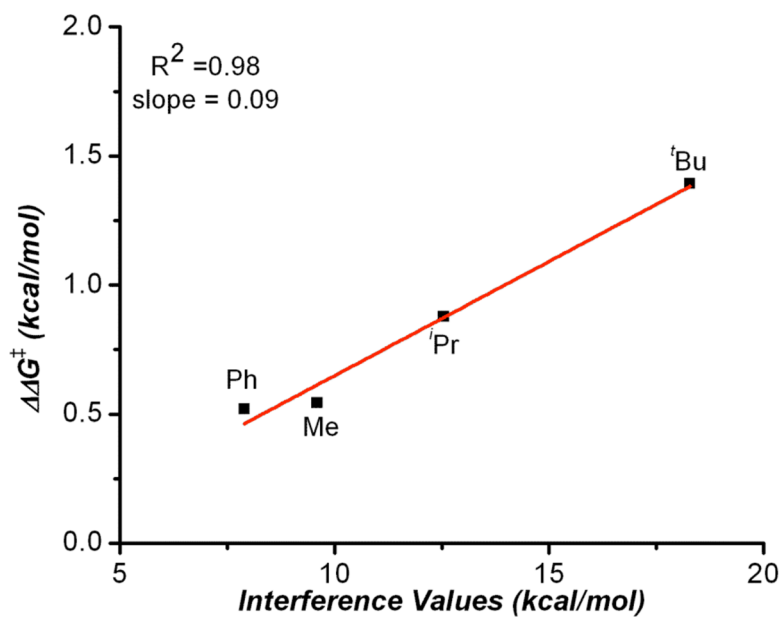


**Figure 3.**  
Comparison of A-values and Charton values for R = CH<sub>2</sub>tBu.

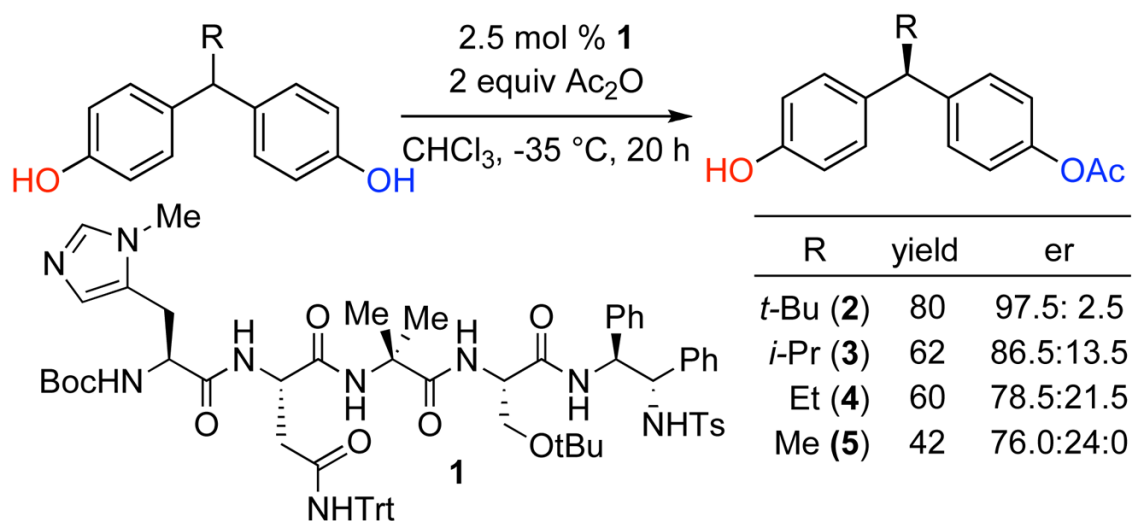


**Figure 4.** Plot of  $\Delta\Delta G^\ddagger$  derived from enantiomeric ratio versus the corresponding A-value.





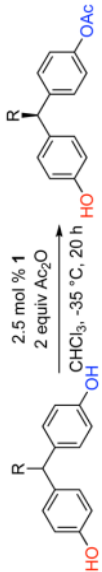
**Figure 5.** Plot of  $\Delta\Delta G^\ddagger$  derived from enantiomeric ratio versus the corresponding interference values.



**Scheme 1.**  
Empirical effect of sterics on the enantioselective desymmetrization of (bis)phenols.

Table 1

Evaluation of various (bis)phenols with catalyst **1** and corresponding common steric parameters.



entry	R	% yield <sup>a</sup>	er(R/S) <sup>b</sup>	Charton value (ν) <sup>c</sup>	A-value (kcal/mol) <sup>d</sup>	<i>P</i> <sup>x</sup> -H (kcal/mol) <sup>e</sup>
1	<i>t</i> Bu	80	97.5:2.5	1.24	4.5	18.29
2	<i>i</i> Pr	62	86.5:13.5	0.76	2.21	12.56
3	Et	60	78.5:21.5	0.56	1.79	---
4	Me	42	76.0:24.0	0.52	1.74	9.60
5	Ph	40	75.0:25.0	0.57	2.80, 2.20	7.90
6	<i>c</i> C <sub>6</sub> H <sub>11</sub>	55	82.5:17.5	0.87	2.20	---
7	1-adamantyl	55	98.5:1.5	1.33	---	---
8	CH <sub>2</sub> Et <sub>2</sub>	80	91.0:9.0	1.28	---	---
9	CH <sub>2</sub> <i>i</i> Bu	45	77.5:22.5	1.34	2.00	---
10	CH <sub>2</sub> <i>i</i> Pr	53	67.5:32.5	0.98	---	---
11	CH <sub>2</sub> Ph	46	71.5:28.5	0.70	1.68	---
12	CHPh <sub>2</sub>	49	85.0:15.0	1.25	---	---

<sup>a</sup>Isolated Yields.

<sup>b</sup>Determined by chiral HPLC analysis.

<sup>c</sup>See reference 8c, 8d.

<sup>d</sup>See reference 11.

<sup>e</sup>See reference 14.