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Computational and experimental structure–reactivity relationships: evidence for a side reaction in Alpine-Borane reductions of *d*-benzaldehydes

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ABSTRACT

Extraordinary stereoselectivity, approaching 100%, has been reported in the reductions of *d*-benzaldehydes by *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane). This is likely because of the extreme size disparity of groups on either side of the carbonyl. Here, we present a structure–reactivity study whereby the reductions of variably substituted *d*-benzaldehydes are explored using highly sensitive measures for enantiomeric excess and relative reactivity. These results are compared to the relative rates predicted from density functional calculations. The results indicate that 2,6-disubstitution adversely affects the stereoselectivity by means of a non-selective reduction via the dehydroboration product of Alpine-Borane, 9-borabicyclo[3.3.1]nonane.

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Stereoselective reduction of prochiral carbonyl-containing compounds is one of the most highly developed classes of asymmetric conversions; however, the substrate range of a particular conversion is often difficult to predict.[1] Stereoselective reactions can suffer an attenuation of selectivity via three primary routes: (1) close competition between diastereomeric transition states, (2) post-reaction racemization through a symmetric intermediate, and (3) the active participation of a non-selective side reaction. Nowhere is this consideration more evident than in stereoselective reductions of prochiral ketones by *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane). The availability of natural olefins bearing stereogenic centers coupled with the reactivity of organoboranes has made asymmetric organoboranes an important source of chirality in stereoselective syntheses. Some of the first examples of chirality transfer via organoboranes performed by Midland et al. illustrated the potential of these compounds to perform stereoselective reductions with high yields and selectivities. In particular, Alpine-Borane was found to reduce *d*-benzaldehydes with very high selectivity, often approaching 100% enantiomeric excess.[2] Disappointingly, further studies on the substrate range of this compound showed it to be much less effective in reducing aralkyl ketones and most dialkyl ketones. Midland subsequently showed that the application of high static pressures to the reaction yielded improved selectivity in most previously intractable reactions, accompanied by a similarly impressive rate enhancement.[3,4] Based on this observation, Midland surmised that the origin of stereoselectivity degradation in the Alpine-Borane reduction of ketones is due to competitive non-selective reduction via 9-BBN, the dehydroboration product of Alpine-Borane (Fig. 1). This hypothesis was later validated by observing the transfer of 9-BBN from Alpine-Borane to competing alkenes in solution.[5,6] Furthermore, Brown et al. found that the exclusion of solvent from the reduction of ketones provided similar gains in selectivity.[7] These observations are consistent with the putative side reaction, given that the volume of activation for dehydroboration (**TS3**) is likely to be large and positive and the relative entropy of solvation for the two dissociation products is likely to be higher than that for the single progenitor species.

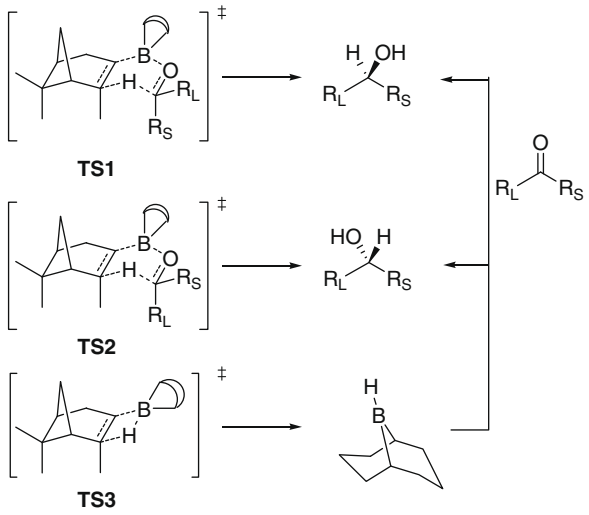

Figure 1. Possible competing rate-determining transition states in the Alpine-Borane reduction of prochiral ketones and *d*-aldehydes.

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The substrate range of Alpine-Borane, however, is far from being well understood. Another key observation lends some insight into the problem: while aralkyl and dialkyl ketones behave unpredictably under Alpine-Borane reduction, ynones are typically reduced faster with higher selectivities, in general, than other classes of ketones.[8–10] This behavior can be understood in the context of the relative steric presence of alkynyl substituents. The two sp-hybridized carbon centers adjacent to the carbonyl significantly attenuate the steric bulk of these substituents near the carbonyl. Of course, the determinants of substrate range are not simply concerned with the relative bulk of the large (R_L) substituent and the small (R_S) substituent on the prochiral ketone. Excess steric bulk in the large substituent appears to attenuate reactivity in the reduction of ynones bearing an α-3° center. As in other Alpine-Borane reductions with attenuated selectivity, a competing non-selective reduction via 9-BBN is thought to result in low selectivities for these substrates.[10] Here, we explore a similar phenomenon in the Alpine-Borane reductions of benzaldehydes. We utilize a very accurate means of measuring relative reactivity in Alpine-Borane reductions. These results are compared to the computed relative rates obtained from density functional calculations. Finally, a very accurate means of measuring enantiomeric excess has been employed with the objective of correlating aberrations in reactivity profiles with a reduction in selectivity. The objectives of these studies are to (1) provide further evidence for the suspected non-selective 9-BBN reduction as a competing side reaction, (2) provide an experimentally validated transition structure for the Alpine-Borane reduction of benzaldehydes, and (3) understand the limitations upon substrate range for these conversions.

We employed a new methodology to determine the relative rates of Alpine-Borane conversion of the 11 representative alkyl-substituted benzaldehydes identified as shown in Figure 2. This method allows for the simultaneous competition of numerous substrates. The strength of this approach lies in the inherently large chemical shift dispersion in ^{13}C spectra. Because the methyl groups upon each substrate aldehyde and product alcohol are resolved at the baseline, we can compare the relative conversions using a quantitative ^{13}C NMR method (see Supplementary data). This method relies upon a simultaneous competition reaction whereby the eleven-substituted substrates denoted in Figure 2 compete for a limited amount of (*R*)-Alpine-Borane. The relative amounts of each alkyl-substituted benzaldehyde were quantified before reaction as detected by distinct methyl resonances. Following reaction, the resulting amounts of alkyl-substituted benzyl alcohols were determined via distinct methyl resonances. The ^{13}C NMR was performed on the initial reactant and resulting product mixtures using calibrated 90° pulse widths and relaxation times that were $5\times T_1$ for the resonance of interest with the longest relaxation time. This value was calibrated using an inversion recovery experiment with calibrated pulse widths. This method was chosen over HPLC detection of product and reactant ratios because HPLC could not resolve each of the eleven reactants and products with baseline resolution.

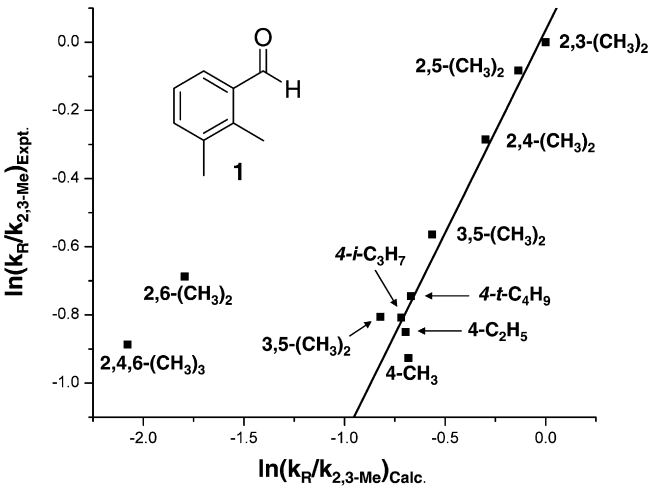

Figure 2. Relationship between experimental and computed relative rates for the (*R*)-Alpine-Borane reduction of alkyl-substituted benzaldehydes using 2,3-dimethylbenzaldehyde (**1**) as a reference substrate.

Numerous comparisons of experimentally determined kinetic isotope effects with those predicted from computational models using density functional theory have validated the use of the B3LYP density functional in arriving at meaningful representations of the transition structure.[11–15] As a point of comparison with our empirical determination of relative rates, we computed the transition structures for preferred *re* attack of (*R*)-Alpine-Borane upon the eleven variably substituted benzaldehydes shown in Figure 2. The reactant aldehydes were also optimized. Frequency calculations upon the reactant and transition structures allowed for the estimation of the relative free energies of activation ($\Delta\Delta G^{\ddagger}$). Using the Eyring equation, the relative rates were derived. The logarithms of computed relative rates were compared with the logarithms of experimentally determined relative rates to give direct comparisons of the relative free energies of activation (Fig. 2). A strong correlation ($R^2 = 0.94$) with a slope near unity (1.13 ± 0.09) was found for all substrates, excluding 2,6-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde. The relative rates for the conversions of these two substrates were well above what might be expected from the correlation between computed and measured relative rates. While these data are somewhat compelling evidence for a side reaction for substrates bearing 2,6-disubstitution, we posited that such a side reaction should lower selectivity in the reduction of the *d*-benzaldehyde analogs of these reactants, if the side reaction is the suspected non-selective 9-BBN reduction of the aldehydes following dehydroboration of (*R*)-Alpine-Borane.

Exploring the selectivity profile for the *d*-benzaldehyde isotopologs of the substrates shown in Figure 2 can be performed in a number of ways. In the current study, we elected to perform these measurements by obtaining ^2H NMR spectra of the resulting alcohol products within a poly-γ-benzyl-L-glutamate matrix.[16,17] This method was chosen because all of the alternative methods have significant drawbacks for this particular measurement: quantitative measurements of the enantiomeric ratio using a chiral HPLC stationary phase are precluded, as the stereogenic center bears two atoms that differ only in isotopic identity. Chiral shift agents are typically challenging because of the simultaneous shift and broadening of the relevant peaks. Finally, the only viable alternative, the construction of Mosher's esters of the resulting alcohols is costly, time consuming, and can suffer from contamination via the minor enantiomer of the Mosher's acid chloride utilized. To ensure quantitative accuracy in the ^2H NMR determinations of enantiomeric ratio, these measurements were carried out using calibrated 90° pulse widths and relaxation times corresponding to greater than $5\times T_1$ for the resonance of the major enantiomer. Overnight acquisitions using a tunable broadband probe on a 400 MHz Varian Unity NMR provide signal-to-noise ratios of at least 20:1 for the minor enantiomer. Thus, the strength of this method resides in the tremendous dynamic range in ^2H signals that can be accessed. Table 1 shows further support for the hypothesis of a non-selective side reaction, as the only substrates with significantly less than 95% ee are the 2,6-dimethyl-*d*-benzaldehyde and 2,4,6-trimethyl-*d*-benzaldehyde.

The effects of alkyl substitution upon the aryl ring can be reasoned to be largely steric in nature. Electronically, 2,4-dimethylbenzaldehyde and 2,6-dimethylbenzaldehyde should be similarly reactive. However, the 2,6-disubstituted analog is found, both

Table 1
Enantiomeric excess and enantiomeric ratios measured for the reduction of variably substituted *d*-benzaldehydes using ^{2}H NMR

Substitution	% ee[a]	er[a]
4-CH_3	96.96% ± 0.11%	64.7 ± 2.6
4-C_2H_5	94.59% ± 0.19%	35.9 ± 1.8
4-*i*-C_3H_7	96.80% ± 0.17%	61.5 ± 4.0
4-*t*-C_4H_9	97.84% ± 0.18%	91.7 ± 7.0
2,3-$(CH_3)_2$	97.45% ± 0.77%	77.6 ± 9.5
2,4-$(CH_3)_2$	95.14% ± 0.09%	40.2 ± 0.7
2,5-$(CH_3)_2$	95.67% ± 0.24%	45.2 ± 1.2
2,6-$(CH_3)_2$	75.40% ± 1.14%	7.1 ± 0.3
3,4-$(CH_3)_2$	96.00% ± 0.15%	48.9 ± 2.8
3,5-$(CH_3)_2$	97.21% ± 0.18%	70.6 ± 5.1
2,4,6-$(CH_3)_3$	88.27% ± 0.22%	16.0 ± 0.3

[a] Errors in % ee and er measurements were computed from signal-to-noise ratios in the spectra.

computationally and experimentally, to be less reactive. Steric occlusion of the 2,6-disubstituted analog is most likely the cause of this effect. In fact, this hypothesis is supported, to some degree, in the transition structures shown in Figure 3. The transition structure for the reduction of 4-methylbenzaldehyde (Fig. 3C) by (*R*)-Alpine-Borane serves as something of a negative control. In this structure, the substituent is well removed from interactions with the isopinocampheyl group and the carbocyclic portion of the 9-BBN moiety. In fact, it can be observed that increasing the steric bulk of a *para*-substituent has negligible effects upon the computed and experimentally determined relative rates (Fig. 2). Upon the addition of a 2-CH_3 substituent, the transition structure must accommodate the methyl group such that it interacts with the carbocyclic portion of the 9-BBN moiety (not shown) or with the proximal axial methyl substituent on the isopinocampheyl group. As is shown in Figure 3A, the transition structure has an energetic preference for the latter, where the C–C separation between these two methyl groups is 4.119 Å. The transition structure for the similarly positioned reduction of 2,6-dimethylbenzaldehyde shows that the addition of another *o*-methyl substituent forces a compromise between the interaction of the substrate with the 9-BBN and isopinocampheyl groups. The result of this compromise is that the occluded methyl group on the isopinocampheyl moiety is closer (3.914 Å) to the 2-CH_3 substituent of the substrate (Fig. 3B).

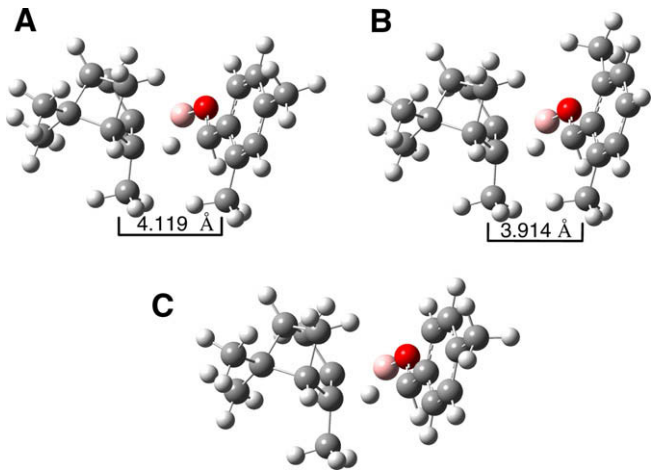

Figure 3. Computed transition structures [B3LYP/6-31+G(d,p)] for the favored *re* attack upon (A) 2,4-dimethylbenzaldehyde, (B) 2,6-dimethylbenzaldehyde, and (C) 4-methylbenzaldehyde. The carbocyclic portion of the 9-BBN moiety has been eliminated for clarity. In each transition structure, the isopinocampheyl group resides on the left, and the substrate resides on the right. The transferred hydrogen atom is represented by an unbonded white sphere near the center of each structure.

The structures shown in Figure 3 offer a satisfactory explanation of the variances in predicted and measured relative rates for substrates bearing 2,6-substitution patterns. The simultaneous interaction of the 2- and 6-methyl groups in 2,6-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde with the isopinocampheyl group enforce a later transition state. The actively participating atoms in the transition state form a six-membered array of atoms. Table 2 contains a summary of the structural parameters from computed transition structures for the (*R*)-Alpine-Borane reduction of the 11 alkyl-substituted benzaldehydes investigated here. The simplest observation that can be drawn from the transition structures and frequency calculations are that, in terms of the evanescent C_{Ipc}–H and nascent B–O bonds, the transition states for the two 2,6-disubstituted benzaldehyde substrates are later than those for all other substrates. These observations are reinforced by the magnitude of the imaginary frequency ($\nu^{\ddagger}$) associated with the reaction coordinate at the saddle point. For these two substrates, $\nu^{\ddagger}$ is larger than those for the other substrates. This observation implies that steric frustration at the transition state enforces a greater participation of hydride motion in the transition state. This supposition is borne out to some degree by observing the reduced mass associated with $\nu^{\ddagger}$ for various substrates. The reduced mass associated with $\nu^{\ddagger}$ for 4-methylbenzaldehyde is 2.18 amu; whereas, the corresponding reduced mass for 2,6-benzaldehyde is 1.96 amu. In summary, the principal parameters describing computed transition structures indicate a later transition state for 2,6-disubstituted substrates. By Hammond's postulate, it may be assumed that the later transition states for these substrates leads to a higher associated free energy of activation, thus allowing for a successfully competing background reaction.

Upon further investigation of Table 2, it may be possible to divide the substrates into three classes. Experimentally, alkyl-substituted benzaldehydes bearing only one *ortho*-substituent are found to be more reactive than other substrates. As one might expect

Table 2
Key structural parameters and imaginary frequencies associated with transition structures [B3LYP/6-31+G(d,p)] computed for favored *re* attack of *R*-Alpine-Borane upon variably substituted benzaldehydes

	(O=)C···H (Å)	C=O (Å)	C_{Ipc}···H (Å)	B···O (Å)	C_{Ipc}···B (Å)	∠Ar–C–H	$\nu^{\ddagger}$ (cm^{-1})
4-CH_3	1.295	1.325	1.378	1.492	1.855	113.5°	745*i*
4-C_2H_5	1.296	1.324	1.377	1.492	1.854	113.6	742*i*
4-*i*-C_3H_7	1.295	1.325	1.377	1.492	1.856	113.5	739*i*
4-*t*-C_4H_9	1.296	1.324	1.376	1.491	1.857	113.5	744*i*
2,3-$(CH_3)_2$	1.307	1.324	1.373	1.493	1.847	115.0	771*i*
2,4-$(CH_3)_2$	1.305	1.325	1.382	1.489	1.854	114.6	794*i*
2,5-$(CH_3)_2$	1.309	1.324	1.378	1.491	1.857	114.4	797*i*
3,4-$(CH_3)_2$	1.295	1.325	1.378	1.490	1.860	113.7	739*i*
3,5-$(CH_3)_2$	1.298	1.324	1.374	1.492	1.856	113.5	743*i*
2,6-$(CH_3)_2$	1.301	1.327	1.408	1.484	1.863	113.1	830*i*
2,4,6-$(CH_3)_3$	1.298	1.329	1.413	1.483	1.866	113.1	840*i*

from Hammond's postulate, the computed transition structures corresponding to these substrates have earlier transition states with respect to the angle about the carbonyl carbon being reduced and the nascent C–H bond. The imaginary frequencies associated with the reaction coordinate motion at the saddle point also fall roughly into three classes. For substrates bearing no *ortho*-substituents, the imaginary frequencies average to $742i\ cm^{-1}$ with little variation in their values. For the second class of reactants, those bearing a single *ortho*-substituent, the imaginary frequencies are all of a significantly larger magnitude, averaging to $787\ cm^{-1}$. Finally, benzaldehydes bearing two *ortho*-substituents have imaginary frequencies averaging to $835\ cm^{-1}$. This suggests that the reduced mass of the reaction coordinate motion at the transition state is dropping as one progresses from class to class. The associated reduced masses from representative members of each class support this hypothesis, as the imaginary frequencies have associated reduced masses of 2.18 amu for 4-methylbenzaldehyde, 2.04 amu for 2,4-dimethylbenzaldehyde, and 1.96 amu for 2,6-dimethylbenzaldehyde. Structurally, these differences can be understood in terms of the most important bond lengths in the transition structures, those corresponding to the forming and breaking C–H bonds. Substrates bearing two *ortho*-substituents have markedly longer C_{Ipc}–H bonds, while those bearing a single *ortho*-substituent have longer (O═)C–H bonds.

The transition structures characterized in Table 2 are qualitatively similar to semi-empirical transition structures reported in earlier studies.[18–20] Both density functional theory and AM1 transition structures differ from the qualitative structures shown in Figure 1 in one important respect: the six-membered scaffold of atoms that are primarily involved in the reaction coordinate at the transition state form more of a half-chair structure instead of a boat-like arrangement. Even with this important difference, the structures shown in Figure 3 exhibit similar non-bonding interactions as those that might be expected from the qualitative structures in Figure 1. Primarily, the axial methyl group upon the isopinocampheyl group appears to be a principal director of stereoselection.

Substrates bearing a single *ortho*-substituent display the highest reactivity toward Alpine-Borane reduction. This finding is puzzling, considering that computed transition structures for the Alpine-Borane reduction of these compounds show moderate coincidence of the *ortho*-substituent and the proximal methyl group on the isopinocampheyl moiety (Fig. 3). This observation raises the possibility of complementarity in stereoselective reactions. The origin of this behavior is not easily understood, given the numerous physical phenomena that determine both reactivity and selectivity: orbital interactions, steric interactions, reaction synchrony, configurational entropy, etc. One possibility is that complementary reactants or catalyst–reactant pairs naturally form complexes that restrict allowable geometries to near-attack conformers (NACs). This explanation has served as an explanation of how enzymes convert binding energy into catalytic power.[21,22]

In this Letter, we have presented the results of an empirical and computational structure–reactivity study that displays a high degree of correlation, excepting substrate benzaldehydes bearing two *ortho*-substituents. These exceptions have been explained using a structure-selectivity experiment, whereby the variably substituted *d*-benzaldehyde isotopologs were investigated as substrates in (*R*)-Alpine-Borane reduction. The *d*-benzaldehyde substrates that contained 2,6-disubstitution were found to be react with significantly impaired selectivity, implying the role of a non-selective side reaction. These results, in conjunction with previous findings, implicate 9-BBN as the non-selective reductant in this side reaction. Computational models of the transition structures for favored *re* attack of (*R*)-Alpine-Borane upon the eleven substrates tested here suggest that the eleven variably substituted benzaldehydes may be parsed into three classes.

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Supplementary data

Supplementary data (experimental procedures, NMR integration results, computational procedures, and energies and geometries of all calculated structures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.109.

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