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Experimental transition state for the Corey–Bakshi–Shibata reduction

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ABSTRACT

Asymmetric reductions of prochiral ketones are important transformations in the syntheses of natural products, pharmaceuticals, and fine chemicals. The Corey–Bakshi–Shibata reduction is unique among hydride transfer reductions in its tremendous substrate range and catalytic nature. Here, a coordinated computational and experimental approach is taken toward understanding the origins of the high selectivity and broad substrate range, which are hallmarks of this reduction.

Amino acids are readily available sources of chirality. Itsuno et al. pioneered the use of valine derivatives as stoichiometric reducing agents to achieve the stereoselective reduction of prochiral ketones.[1,2] Following a brief mechanistic study of the reduction of ketones via these derivatives, Corey et al. concluded that these amino acid derivatives could be used catalytically with stoichiometric borane to reduce prochiral ketones with high selectivity.[3] Further refinements concerned with optimizing enantioselectivity and catalyst stability led to the mainstay of oxazaborolidine reduction catalysts, Me–CBS (**1**)[4], a catalyst that has been heavily utilized in natural product synthesis[5] and employed in some reported large-scale processes.[6] Demanding reductions have also led to the development of later generation CBS catalysts and to the use of less common reductants.[5]

While excellent mechanistic work by Corey's group[3,4,7,8] and others[9–12] has yielded a satisfying picture of the catalytic cycle for CBS reductions (Fig. 1), an experimentally-validated picture of the transition structure corresponding to the rate-determining step is lacking. ^{13}C kinetic isotope effects (KIEs) have been heavily utilized over the last decade in refining mechanistic understanding and in gaining detailed insight into transition structures. Here, we report ^{13}C KIEs measured using a recently developed method[13] and ^{13}C KIEs computed from a model of the transition structure for the reduction of 2′,5′-dimethylphenyl isopropyl ketone. The experimentally corroborated computational model for the preferred *Si* attack transition structure serves as a basis for understanding the origins of stereoselection in this reduction system.

The transition structure for the rate-limiting step in the (*S*)-Me–CBS-catalyzed borane reduction of 2′,5′-dimethylphenyl isopropyl ketone has been constructed using experimentally determined ^{13}C KIEs and computationally derived transition structures. The ^{13}C KIEs were determined using a methodology that is capable of yielding individual KIEs upon enantiotopic groups. In the current system, the isopropyl substituent provides two enantiotopic methyl groups. This method is performed in a way similar to that developed by Singleton and Thomas:[14] Remaining reactant is isolated from a high conversion reaction (~80–90%). The reactant is then desymmetrized using the same highly selective reaction being studied. Quantitative ^{13}C NMR is then used to compare relative amounts of ^{13}C label in each position in both the reisolated and desymmetrized reactant and desymmetrized stock reactant. NMR assignments of the pro-*R* and pro-*S* methyl groups are made using chemical shifts computed by the CSGT[15] methodology and the IGAIM[16] variation upon a fully optimized B3LYP/6-31+G(d,p) model of the anticipated *S* enantiomer of the benzylic alcohol product. The key benefit of this isotope effect methodology is that any pair of enantiotopic groups can serve as probes of the symmetry breaking process.[17] The results of four independent measurements from reactions taken to 84.4%, 85.8%, 85.8%, and 87.7% conversion are shown in Figure 2A.

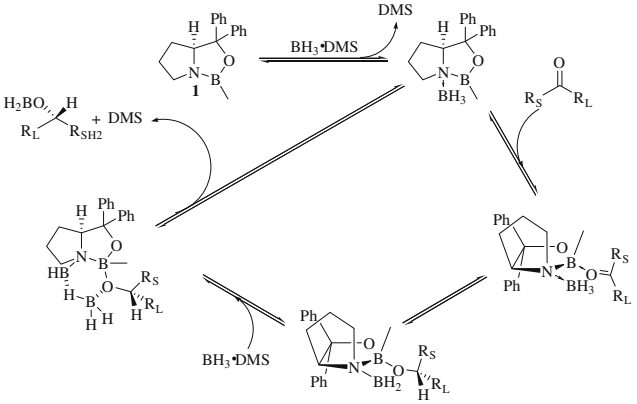

Figure 1. Proposed catalytic cycle for the CBS reduction.

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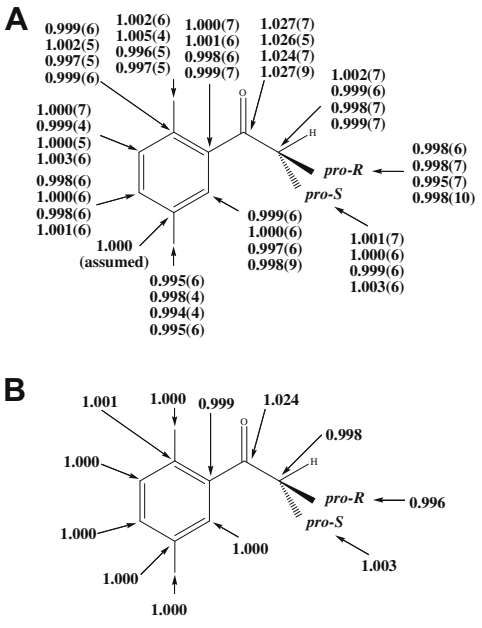

Figure 2. (A) Experimental ^{13}C KIEs (k_{12C}/k_{13C}) for the (*S*)-Me–CBS-catalyzed borane reduction of 2′,5′-dimethylphenyl isopropyl ketone. (B) Computed KIEs based on the [B3LYP/6-31+G(d,p)] transition structure for *Si* attack.

Computed ^{13}C KIEs (Fig. 2B) are generated using the Bigeleisen equation[18] using input from frequency calculations upon corresponding isotopologs of 2′,5′-dimethylphenyl isopropyl ketone and the transition structure. The computed values presented here contain a simple Bell infinite barrier tunnel correction.[19]

Several conclusions regarding the borane reduction of 2′,5′-dimethylphenyl isopropyl ketone catalyzed by **1** can be drawn from the measured and computed KIEs shown in Figure 2. The substantial KIE at the carbonyl carbon and excellent agreement between the measured and computed KIE values suggest that the rate-determining step for this conversion is the hydride transfer step. Furthermore, from the computed transition structure for favored *Si* attack (Fig. 3A), it appears that the phenyl groups residing on the CBS catalyst (**1**) have little direct impact upon the steric constraints that dictate the placement of the small (R_S) and large (R_L) substituents of the ketone. A comparison of the computed structures and stylized representations of the transition structures for

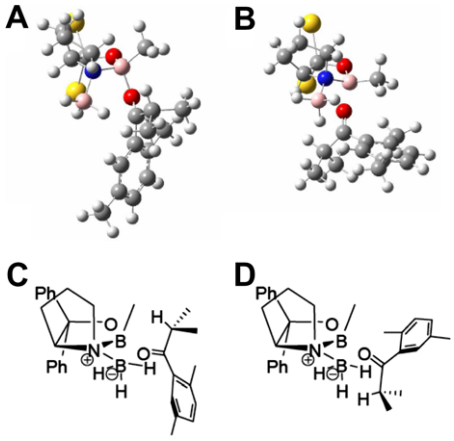

Figure 3. Computed transition structures [B3LYP/6-31+G(d,p)] for (A) favored *Si* attack and (B) disfavored *Re* attack. Phenyl groups on the (*S*)-Me–CBS catalyst are indicated by gold spheres. Stylized transition structures for (C) *Si* and (D) *Re* attack.

Table 1
Key descriptive parameters in the TSs for *Re* and *Si* attack

Structural element	*Si* attack (preferred)	*Re* attack (disfavored)
C(=O)···H	1.8933 Å	1.9824 Å
C=O	1.2715 Å	1.2634 Å
B···H	1.2453 Å	1.2395
B···O	1.5887 Å	1.6410 Å
N···BH_3	1.6193	1.6119
$\angle R_S$–C(=O)–R_L	120.07°	120.20°
$\nu^{\neq}$	262*i*	173*i*

Si (Fig. 3A and C) and *Re* (Fig. 3C and D) attack suggests that the phenyl groups serve to constrain the conformation of the bicyclic CBS catalyst which further dictates α-coordination of the ketone to the catalyst. Finally, as is shown in Table 1, the imaginary frequency corresponding to motion along the reaction coordinate at the transition structure is rather low for what is effectively a hydride transfer (262*i* cm^{-1}). The simplest explanation for this result is that heavy atom motion represents a substantial portion of the reaction coordinate motion; however, the reduced mass for this motion is only 1.84 amu compared to a value of 2.27 amu for the DIP-Cl reduction of 4′-methylphenyl isopropyl ketone ($\nu^{\neq}$ = 776*i* cm^{-1}). Obviously, it is the relatively small negative force constant, rather than a larger reduced mass, that is responsible for the relatively low imaginary frequency in the CBS reduction.

Table 1 summarizes the important structural parameters that characterize transition structures computed for both *Re* and *Si* attack. Most notable are the differences in the lengths of the nascent C(=O)–H bond formed between the carbonyl and the attacking hydride and the B–O bond forming between the catalyst and the oxygen of the substrate carbonyl. The transition structure for the unfavored *Re* attack has structural features that suggest a later dividing surface for this reaction. Such a situation is entirely consonant with expectations in stereoselective reactions where steric interactions are responsible for precluding a particular reaction channel.

The subtle ^{13}C KIEs at the prochiral methyl groups of the substrate exhibit agreement with values computed from the transition structure for *Si* attack. The simplest view of these measurements is that the pro-*S* methyl group exhibits a normal isotope effect, while the pro-*R* methyl group exhibits an inverse KIE. Considering that there are no significant changes in bonding at the prochiral methyl groups, the inverse KIE upon the pro-*R* methyl group is best classified as a steric isotope effect.[20] In contrast, the origin of the normal KIE upon the pro-*S* methyl group is likely due to a small electronic effect: The pro-*S* methyl group is placed syn-periplanar to the nascent C–H antibonding orbital (σ^*) being formed. Analogous to the effect observed by Cieplak, some mixing of the C–C bonding orbital with the unfilled σ^*_{C-H} orbital is likely.[21] Such an interaction would have a normal contribution to the KIE observed at the pro-*S* methyl group. The small normal contribution to this value may serve to offset a general steric occlusion at the small group (R_S) occurring as a result of steric contributions from both the *B*-Me group and the large group (R_L) on the ketone. The computed structure for *Re* attack of the hydride places the *pro*-R group antiperiplanar to the nascent C–H bond. It is somewhat satisfying that the trends in the ^{13}C KIEs upon the enantiotopic methyl groups are reversed for this computed structure, yielding a more normal KIE for the *pro*-R methyl group.

At first glance, it would appear that the steric demands responsible for a highly organized transition structure in this system are obvious: Conformational rigidity of the bicyclic CBS catalyst is enhanced by the geminal diphenyl substitution pattern. The conformation of the bicycle then enforces α-coordination (*exo*) of the ketone to the catalyst. The *B*-alkyl substituent in the catalyst then

provides a steric presence that enforces the relative placement of the large (R_L) and small (R_S) substituents of the prochiral ketone in the transition structure (Fig. 3).

Several observations suggest that the above reasoning is perhaps too simplistic. Numerous analogs to the (*S*)-Me–CBS (**1**) catalyst exist. In testing these analogs, the most often performed reduction is that of acetophenone to 1-phenylethanol. The two predominant variations upon **1** are alterations in the geminal substitution at the carbinol center and the boron substituent. In the reduction of acetophenone, the boron substituent seems to play little role in stereoselection. With H, Me, Et, and *n*-Bu as substituents giving nearly quantitative yields and enantiomeric excesses of 97%[3], 96.5%[4], 96%[22], and 96%[22], respectively. There does, however, appear to be a marked effect of the carbinol substitution pattern upon enantioselectivity, with H, Ph, β-Np, α-Np, 2′-methylphenyl, 2′-methoxyphenyl, and thiophenyl groups yielding enantiomeric excesses of 77%, 97%, 98%, 62%, 76%, 28%, and 82%.[5,23] While it is likely that the simple unsubstituted carbinol lacks the conformational rigidity necessary for stereocontrol, something more complex is at work in the cases of the α-Np, 2′-methylphenyl, 2′-methoxyphenyl, and thiophenyl carbinol substitution. The first three substituents possibly interfere with coordination of the ketone to the catalyst as it enters the catalytic cycle. A potential partitioning of the substrate between uncatalyzed and catalyzed pathways may be responsible for low enantioselectivities in these cases. While thiophenyl is perhaps slightly less obtrusive than phenyl, this small change in steric presence may be only a secondary reason for decreased selectivity. More likely is that the thiophenyl group is capable of coordinating the reductant and may essentially reduce the concentration of active catalyst-reductant complex in the active catalytic cycle.

Part of the role of the carbinol substituents is perhaps hinted at in the ^{13}C KIE at the 5′-methyl position. While all other KIEs are consistently within one standard error of the computed values, the 5′-methyl group displays a consistent, if marginally significant, deviation from the predicted ^{13}C KIEs. If this difference is an accurate reflection of what is occurring at the transition state, then it may hint at an unexpected origin of stereoselectivity in the CBS system. Computational models of the transition state tend to steer thinking away from the more correct *ensemble* picture of the transition structure. It is possible that torsional motion between the aryl ring and carbonyl carbon places the 5′-methyl group in near incidence with one of the geminal phenyl groups on the catalyst. A mixed torsional mode at 23 cm^{-1} involves significant rotation of the substrate aryl group in the computed transition structure for preferred *Si* attack, signaling that the ensemble of transition structures germane to a free energy description of the transition state may contain members with some steric interaction between the 5′-methyl group and the axial phenyl group in the catalyst.

In the simplest terms, the origins of reactivity in the CBS reduction are well understood: The endocyclic boron serves as a Lewis acid activator of the electrophile, while the endocyclic nitrogen local to the adjacent ring activates the nucleophile (reductant) via donation of its lone pair. While this thermodynamic argument is satisfying, further inspection suggests that the CBS catalyst may employ strategies borrowed from alcohol dehydrogenases to lower the reaction barrier for hydride transfer. As stated before, the imaginary frequency corresponding to reaction coordinate motion at the transition state is lower than one might anticipate for hydride transfer (262*i* cm^{-1}). Furthermore, the diminution of this frequency does not result from a large reduced mass but rather from a small negative force constant. Such a situation infers that the transfer is rather adiabatic. The small primary kinetic isotope effect (k_H/k_D = 1.7)[24] is also indicative of a largely adiabatic transfer. This value is in contrast to those observed for the borane reduction of ketones: (k_H/k_T = 6.22–11.1),[25] which correspond to deuterium KIEs of approximately 5.08–9.06 using a mass conversion based solely on the square root of the masses transferred. Adiabatic transfers are the result of strong electronic mixing of the hydride donor and acceptor states, typically mediated by hydrogen bonding interactions, electrostatic interactions, or interactions between filled and unfilled orbitals. The bonding changes that occur during the rate-determining hydride transfer step involve changes in the latter two types of interactions during the hydride transfer. The hydride transfer step results in the reduction of the number of centers bearing formal charge. Analogous to the simultaneous activation of both nucleophile (BH_3) and electrophile (ketone) is the simultaneous general acid activation of the electrophile (aldehydes) and conformational activation of the nucleophile (NADH) in alcohol dehydrogenases, which essentially weakens the labile C–H bond upon NADH. The intrinsic primary isotope effect for the horse liver alcohol dehydrogenase-catalyzed reduction of benzaldehyde is generally assumed to be around k_H/k_D = 3.5; however, measured values and values determined from simulated kinetic traces have been found to be 1.9 and 2.8, respectively.[26] Unfortunately, apt comparisons with the uncatalyzed reaction are lacking.

In conclusion, we have measured ^{13}C KIEs for the CBS reduction of 2′,5′-dimethylphenyl isopropyl ketone and computed a model transition structure that yields KIEs that are firmly in agreement with the experimental measurements. We have also presented an isotope effect methodology by which ^{13}C KIEs may be measured for each individual enantiotopic group in reactions where symmetry breaking makes the groups inequivalent. Finally, the results of our experimental and computational work have suggested new potential strategies for controlling selectivity in asymmetric catalytic reactions and have highlighted the similarities and differences between enzyme and small molecule catalysis.

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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.2009.01.033.

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