JOC The Journal of Organic Chemistry

Article

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Lewis Acid Catalysis and Ligand Exchange in the Asymmetric Binaphthol-Catalyzed Propargylation of Ketones

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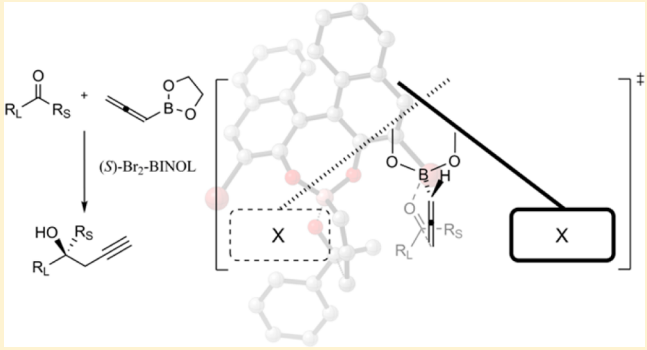
Supporting Information

ABSTRACT: 1,1′-Bi-2-naphthol (BINOL)-derived catalysts catalyze the asymmetric propargylation of ketones. Density functional theory (DFT) calculations show that the reaction proceeds via a closed six-membered transition structure (TS) in which the chiral catalyst undergoes an exchange process with the original cyclic boronate ligand. This leads to a Lewis acid type activation mode, not a Brønsted acid process, which accurately predicts the stereochemical outcome observed experimentally.



INTRODUCTION

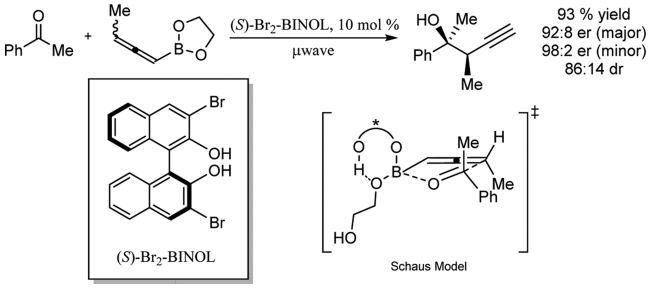
Homopropargylic alcohols are useful synthetic intermediates.[1−5] Despite this, their preparation remains synthetically challenging. Propargylic reagent rearrangement to the allenic analogues can occur which yields a mixture of the β-acetylenic and α-allenic carbinols.[6,7] Early asymmetric propargylation reactions made use of chiral allenyl metal reagents,[8] and more recently, catalytic methods have been reported.[9]

In 2011, Schaus and Barnett reported the use of a BINOL-derived chiral diol as an effective promoter of ketone propargylation to give the corresponding homopropargylic alcohols in excellent yield and enantioselectivities (Scheme 1).[10] Furthermore, the reaction employs an allenylboronate which offers complete control over regioselectivity.

However, it is unclear how the chiral diol catalyzes the reaction. To explain the observed diastereoselectivity in the reaction of racemic boronates with acetophenone in the presence of (*S*)-Br$_2$-BINOL, Schaus proposed a mechanism proceeding via a six-membered cyclic transition structure (TS) in which the chiral diol reacts with the cyclic boronate to give a binaphthol-associated boronate (Scheme 1, Schaus Model). The diastereoselectivity was suggested to originate from the preference for the methyl groups of the ketone and boronate to be antiperiplanar in the TS. Our previous work, which examined similar chiral diol-catalyzed reactions, showed that binaphthol-associated boronates were responsible for the catalytic effects observed.[11−13] However, only a Lewis acidic species derived from the complete displacement of the original ligand(s) can explain the experimental observations, not a Brønsted acid catalyzed pathway in which the original ligand and the diol are both covalently attached to a boron atom.[12]

Our recent study of the propargylation of aldehydes, a reaction developed by Antilla et al.[14] and Reddy,[15] demonstrated that Brønsted acid catalysis could lead to high enantioselectivity in this process.[16] The BINOL-derived phosphoric acid was able to form two distinct hydrogen bonds to the reacting system and so influence the enantioselectivity of the process. The ketone propargylation developed by Schaus and Barnett[10] is catalyzed by a BINOL-derived diol and not a phosphoric acid but represents a related overall transformation. Herein, we report the results of DFT calculations that provide a mechanistic understanding of this process. Our calculations suggest the reaction proceeds via a Lewis acid type activation mode in which the original boronate ligand is completely displaced by the chiral diol, not by Brønsted acid activation by either the model in Scheme 1 or a process related to the aldehyde reaction of Antilla and Reddy.

Scheme 1. Asymmetric Propargylation of Ketones[10]



Received: July 24, 2013
Published: August 15, 2013

dx.doi.org/10.1021/jo401611q | J. Org. Chem. 2013, 78, 8796−8801

The Lewis acid pathway accurately reproduces the experimentally observed enantioselectivity.

COMPUTATIONAL DETAILS

The B3LYP density functional[17,18] and split-valence polarized 6-31G** basis set[19,20] were used for all geometry optimizations. All activation free energies are quoted relative to infinitely separated reagents. Quantum mechanical calculations were performed using Gaussian03 (Revision E.01).[21] Single-point energies were taken using the M06-2X density functional[22] and LACVP** basis set,[23] using the Jaguar program (version 7.6).[24] This energy was used to correct the gas-phase energy obtained from the B3LYP calculations.[25,26]

Free energies in solution were derived from gas-phase optimized structures (B3LYP/6-31G**) by means of a single-point calculation using M06-2X/LACVP** with the polarizable continuum model (PCM),[27] as implemented in the Jaguar program (version 7.6). These values were used to correct the Gibbs free energy derived from the B3LYP calculations.

RESULTS AND DISCUSSION

The investigation of uncatalyzed ketone allenylboration identified two unique TSs with the ketone phenyl group positioned either pseudoequatorially or pseudoaxially: **TS-1** and **TS-2**, respectively (Figure 1). The most favorable TS was found to be **TS-1**, with **TS-2** destabilized by steric interactions between the cyclic boronate and the ketone phenyl group. The activation free energy ($\Delta G^{\ddagger}$) of **TS-1** was calculated to be 24.1 kcal mol^{-1} when evaluated using M06-2X/6-31G**.

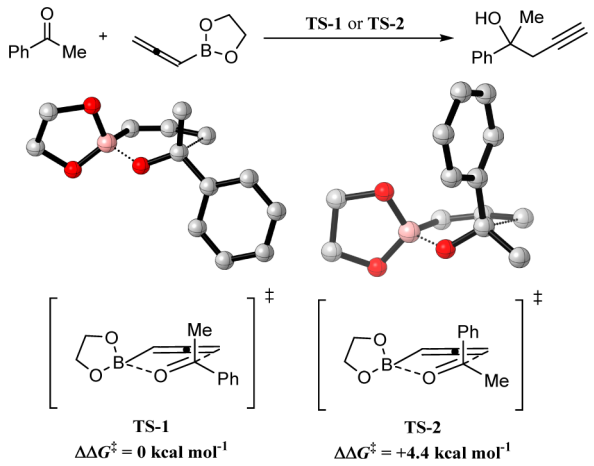


Figure 1. Uncatalyzed TSs for ketone allenylboration. Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/6-31G**. Noncritical hydrogen atoms are omitted for clarity.

To account for the observed enantioselectivity in the catalyzed reaction, the possibility of ligand exchange between the chiral diol and boronate ligand was investigated. The thermodynamic stabilities of the chiral boronates were calculated, and it was found that **1** should be the predominant chiral boronate in the reaction mixture, in agreement with our previous work[11−13] (Scheme 2). Even though **2** is present in lower concentrations than **1**, its Lewis acid catalysis may be more effective than the Brønsted acid catalysis of **1**. This thermodynamic calculation by itself, therefore, does not allow us to decide which is the preferred mechanism. A similar ligand exchange process has been reported for which the higher energy Lewis acid catalyzes the major pathway for a reaction.[12]

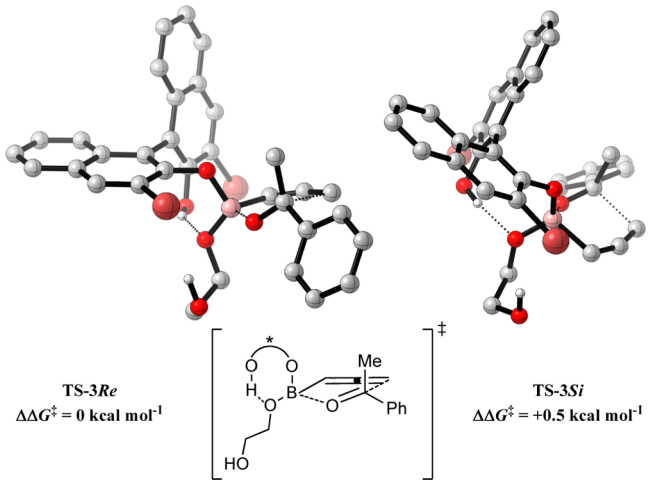


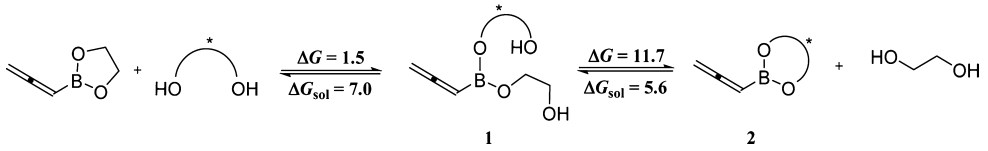
Figure 2. Competing TSs for the reaction between **1** and acetophenone. Geometries were obtained from B3LYP/6-31G** and single-point energies from M062X/LACVP**.

Table 1. Interatomic Distances for Key TSs

	interatomic distance (Å)	
	C−C	B−O
TS-1	2.12	1.49
TS-3*Re*	2.07	1.48
TS-3*Si*	2.06	1.48
TS-4*Re*	2.03	1.47
TS-4*Si*	2.03	1.46

The activation free energy for the reaction of **1** and acetophenone was found to be 16.5 kcal mol^{-1} when evaluated using M06-2X/LACVP**, which is 7.7 kcal mol^{-1} lower than that of the uncatalyzed process. This can be attributed to a Brønsted acid type activation mode in which the remaining catalyst hydroxyl group forms a hydrogen-bonding interaction to the original boronate ligand oxygen (Figure 2). This activates the boron center, leading to a stronger association of the ketone and a tighter TS than the corresponding uncatalyzed reaction (Table 1). However, a comparison of **TS-3*Re*** and **TS-3*Si***, which both involve the (*S*)-BINOL-derived catalyst, indicates that the reaction should proceed to give the *R* propargylic alcohol, whereas the *S* enantiomer is observed experimentally. The preference for **TS-3*Re*** over **TS-3*Si*** can be attributed to an

Scheme 2. Boronate Ligand Exchange Energetics[a]



[a]Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/LACVP**. Free energies are shown in kcal mol^{-1}.

dx.doi.org/10.1021/jo401611q | J. Org. Chem. 2013, 78, 8796−8801

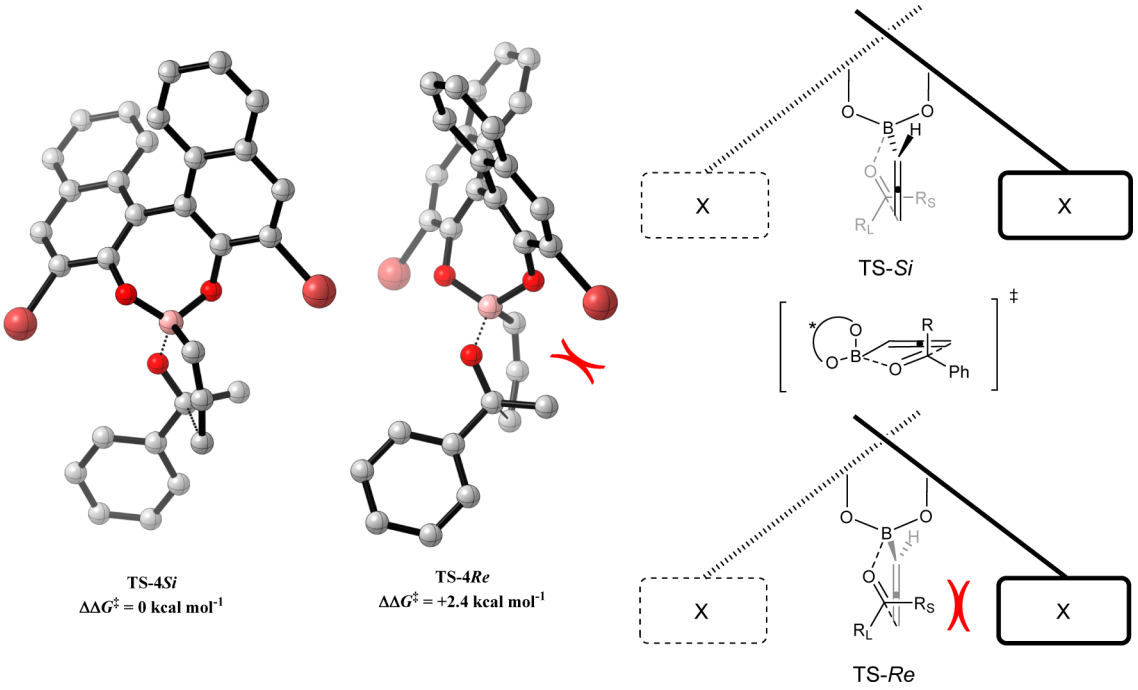


Figure 3. Competing TSs for the reaction of **2** and acetophenone. Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/LACVP**. The interaction of the R group with the chiral ligand in the *Re*-face attack destabilizes this transition state, and so *Si*-face attack is preferred.

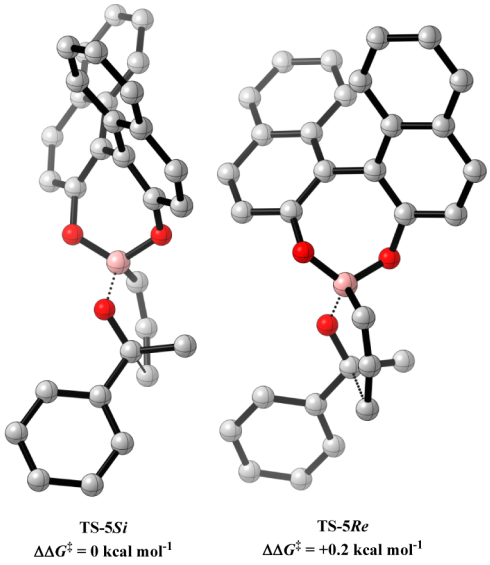


Figure 4. Competing TSs for the propargylation of acetophenone with BINOL as the catalyst. Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/LACVP**.

unfavorable interaction between a catalyst bromine atom and the carbon atom at the allenylboronate α-position in **TS-3*Si***. A total of 77 unique TSs were located for this flexible mode of activation, of which **TS-3*Re*** and **TS-3*Si*** were the lowest in energy (see the Supporting Information). The activation mode in which the catalyst protonates the carbonyl oxygen rather than the original cyclic boronate ligand was also considered. This pathway was found to be 11.3 kcal mol^{-1} higher in free energy than **TS-3*Re***, in agreement with our previous studies that found ligand protonation by the catalyst and carbonyl oxygen coordination to boron to be preferred over simultaneous carbonyl oxygen protonation and coordination to boron.[16,26]

The activation free energy for the reaction of **2** and acetophenone (**TS-4*Si***, Figure 3) was calculated as 9.9 kcal mol^{-1} when evaluated using M06-2X/LACVP**, which is lower than the barrier for both the uncatalyzed reaction and **TS-3*Re***. This pathway corresponds to Lewis acid activation and proceeds via the tightest TS of all mechanisms examined (Table 1). The cyclic boronate **2** is nonplanar, preventing delocalization of the oxygen lone pairs into the empty boron p orbital, leading to a higher Lewis acidity relative to both **1** and the original boronate. **TS-4*Si*** was found to be favored relative to **TS-4*Re*** by 2.4 kcal mol^{-1}, which agrees with the experimental data. Using the calculated Boltzmann ratios of both TSs at 333 K, the predicted er is 97.5:2.5, in close agreement with the observed experimental outcome (97:3 er).

By assuming that the achiral boronate, **1**, and **2** are in equilibrium, Curtin–Hammett conditions must apply and, therefore, the favored pathway is determined by the absolute energies of the TSs.[28] In the gas phase, these conditions indicate that the preferred pathway is **TS-3*Re*** by 5.2 kcal mol^{-1} relative to **TS-4*Si*** (see the Supporting Information).

However, due to the more polarized intermediates and transition structures relative to the starting materials, solvation effects must be considered in order to accurately reflect experimental conditions. The reaction was experimentally performed neat, and therefore the solvation model for acetophenone was used, which while not completely describing the solvation effects of the reaction mixture gives a more accurate description of the reaction conditions than the gas phase. Under Curtin–Hammett conditions, solvation shows that **TS-4*Si*** is the preferred pathway by 2.9 kcal mol^{-1} relative to **TS-3*Re***. This reversal in pathway preference highlights the importance of considering solvent effects when investigating competing organic reactions.[29] Extension of the basis set to the

dx.doi.org/10.1021/jo401611q | J. Org. Chem. 2013, 78, 8796–8801

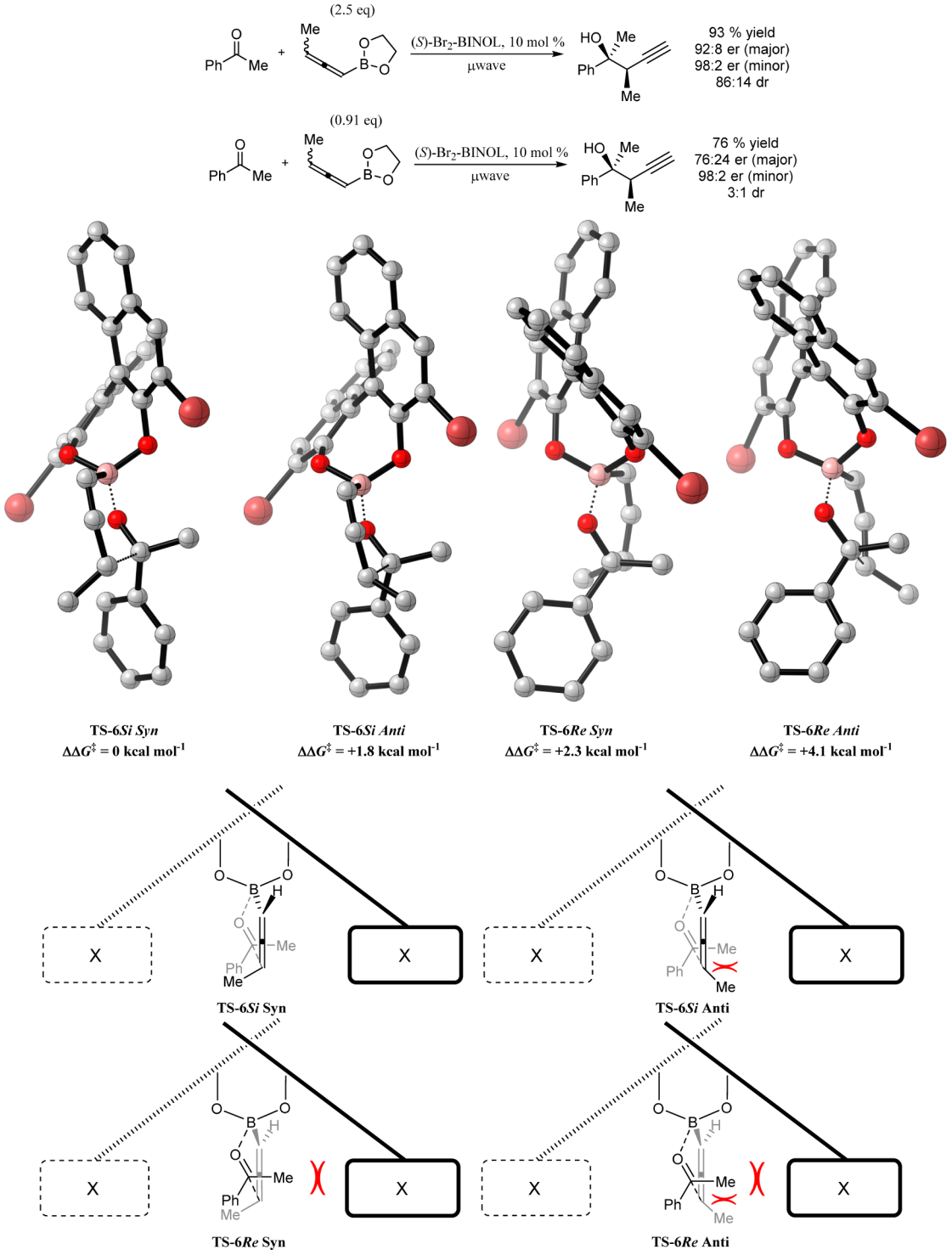


Figure 5. Competing TSs for the kinetic resolution reaction of racemic allenylboronates. Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/LACVP**.

larger 6-311+G** increased the absolute free energies of the TSs but the lowest energy pathway, in both the gas and solution phases, remained the same (see the Supporting Information).

Solvation of **TS-4*Re*** and **TS-4*Si*** led to a decrease in relative free energy of just 0.6 kcal mol^{-1}. This small change in solvation shows that gas-phase calculations are a reasonable approximation for competing TSs within the same reaction mechanism. This can be attributed to similar levels of charge development in these TSs.[16]

The observed selectivity can be rationalized by considering a projection of the catalyst down the central carbon−carbon single bond (Figure 3). The ketone methyl group occupies the axial position, clashing with the catalyst bromine atom in the case of **TS-4*Re***. In **TS-4*Si***, this methyl group is placed in the catalyst empty pocket at the rear of this projection, stabilizing **TS-4*Si*** relative to **TS-4*Re***. Calculations were also performed to

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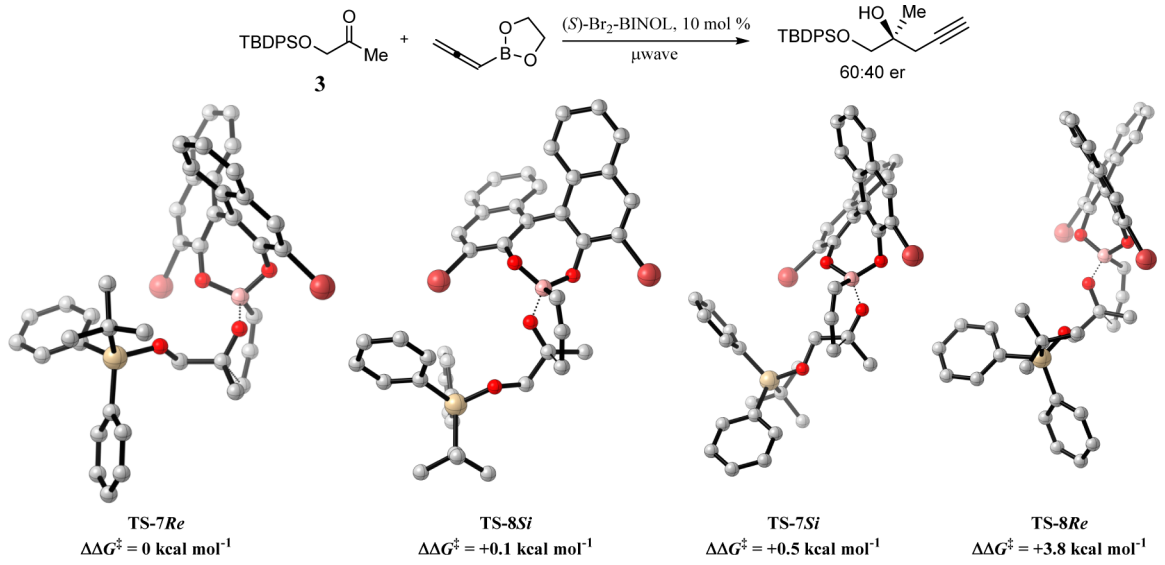

Figure 6. Competing TSs for the propargylation of **3**. Geometries were obtained from B3LYP/6-31G** and single-point energies from M06-2X/LACVP**.

examine the reaction of the ethyl rather than the methyl ketone, to further validate the qualitative model presented in Figure 3 (see the Supporting Information). Experimentally, a 98:2 er was observed, and from our calculations, the er was calculated to be 98:2 at 333 K.

Heating will encourage the C−C bond forming step to go backward as well as forward. The two diastereomeric product complexes, formed after C−C bond formation, were calculated to be within 0.3 kcal mol^{-1} of each other in solution (see the Supporting Information). Therefore, very low levels of enantioselectivity would be observed if the reaction were to occur under thermodynamic control.

Furthermore, examination of the full catalytic cycle revealed that ketone propargylation via boronate **2** and subsequent chiral catalyst release has a $\Delta_r G_{sol}$ value of −14.0 kcal mol^{-1} (see the Supporting Information). The product, therefore, acts as a thermodynamic sink for the reagents and, consequently, under the standard conditions the reaction proceeds under kinetic control via **TS-4*Si***.

The case in which the (*S*)-Br$_2$-BINOL catalyst was replaced by (*S*)-BINOL was also examined. Removal of the 3- and 3′-substituents reduces the enantioselective effect of the catalyst dramatically, and the observed experimental enantiomeric ratio was reported to be 52:48. Our qualitative model predicts that removal of the 3- and 3′-groups should decrease the steric clash between the catalyst and axial ketone methyl group, lowering the enantioselectivity. **TS-5*Si*** and **TS-5*Re*** show that this trend is correct, with the energy difference between the TSs falling from 2.4 kcal mol^{-1} to just 0.2 kcal mol^{-1} (Figure 4).

Schaus also reported an interesting kinetic resolution process in which an excess of the racemic boronate was reacted with acetophenone to give the *S* propargylic alcohol as one diastereomer preferentially (Figure 5). The preferred diastereomer was the *syn*-propargylic alcohol with respect to the allenyl substituent and hydroxyl group. **TS-6*Si Syn*** was found to be the lowest energy TS, which correctly explains the enantioselectivity and diastereoselectivity observed experimentally. Using the qualitative model described above, this TS is preferred, as it places the axial methyl group into the catalyst empty pocket. The diastereoselectivity arises from the preference for the methyl groups of both the allenylboronate and ketone to be *anti* in the TS. **TS-6*Si Anti*** and **TS-6*Re Syn*** were found to be 1.8 and 2.3 kcal mol^{-1} higher in energy than **TS-6*Si Syn***, respectively, which accounts for the larger er in comparison to the dr.

These results indicate that the diastereoselectivity is primarily controlled by the preference for the ketone and allenylboronate methyl groups to be *anti* in the TS, and therefore, the catalyst structure has only a minimal effect on the diastereoselectivity. Schaus reported that upon changing the catalyst to achiral biphenol, which lacks the 3- and 3′-substituents, a change of only 10% de was observed. However, changing the allenyl substituent from a methyl to an isopropyl group gave effectively only one diastereomer due to the increase in steric bulk of the alkyl groups, strengthening the preference for the *anti* arrangement in the TS. Use of BINOL, which lacks the 3- and 3′-substituents, resulted in a dramatic reduction in er from 97:3 to 52:48 (vide supra). Therefore, the sense of enantioselectivity is controlled by the catalyst structure and the diastereoselectivity is predominantly the result of the allenylboronate steric demands.

Extended reaction time and an acetophenone excess afforded the propargylic alcohol in reduced yield and dr and lower er in the case of the major diastereomer (Figure 5). This can be rationalized by considering the competing TSs. **TS-6*Si Syn*** will consume one enantiomer of the racemic boronate to afford the same dr and er as before. However, the remaining enantiomer of the boronate will then react via **TS-6*Si Anti***, which is now the lowest energy TS, eroding the dr but reinforcing the er of the minor diastereomer. **TS-6*Re Syn***, which is 0.5 kcal mol^{-1} higher in energy than **TS-6*Si Anti***, leads to an erosion of the er of the major diastereomer but not the dr.

To further test our model, TSs were located to examine the reaction of acetophenone with **3** (Figure 6). This substrate was reported to yield a 60:40 er in the presence of (*S*)-Br$_2$-BINOL, the lowest ratio of all ketones tested (er was increased to 90:10 by exchanging Br$_2$-BINOL for 9-anthracyl-BINOL). Our calculations indicate that the lowest energy TS is **TS-7*Re*** with the ketone methyl group in the equatorial position. **TS-8*Si***, in which the methyl group occupies the axial position, is

dx.doi.org/10.1021/jo401611q | *J. Org. Chem.* 2013, 78, 8796−8801

0.1 kcal mol^{-1} higher in energy than **TS-7*Re***. Using the qualitative model developed, the loss of selectivity can be rationalized in terms of the lower steric demands of the methyl ketone substituent relative to acetophenone, which reduces the energetic penalty of this group occupying the axial position. By occupying the equatorial position in the *Re* TS, the ketone methyl group avoids the steric interaction with the catalyst bromine substituent, lowering the energy of **TS-7*Re*** relative to **TS-8*Si*** and eroding the er. Unlike aromatic side chains, the TBDPS protecting group is able to find a position that avoids the catalyst bromine in **TS-7*Si*** and so the energy of this TS is similar to that of **TS-7*Re***. If the bromine is replaced with a larger group, such as a 9-anthracyl substituent, this interaction should be reinforced and so the enantiomeric ratio should increase. This is consistent with the experimental data reported by Schaus for this reaction.[10]

CONCLUDING REMARKS

In conclusion, DFT calculations suggest that asymmetric ketone propargylation proceeds via a Lewis acid catalyzed process through a closed six-membered TS in which the chiral catalyst undergoes an exchange process with the original cyclic boronate ligand. While the thermodynamically preferred chiral boronate originates from monosubstitution, complete loss of the original boronate ligand results in the active catalyst species, accounting for the correct sense and level of enantioselectivity. We have also provided a qualitative model (Figure 3) which accurately predicts the observed enantioselectivity and should aid the design of new asymmetric methodology involving this mode of activation.

ASSOCIATED CONTENT

Supporting Information

Text, a figure, tables, and a complete list of authors in the Gaussian03 reference. Cartesian coordinates, energies and number of imaginary frequencies of all stationary points, and values of imaginary frequencies of all transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the EPSRC for funding and Unilever.

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