Article

Understanding the Mechanism of the Asymmetric Propargylation of Aldehydes Promoted by BINOL-Derived Catalysts

Matthew Neil Grayson, and Jonathan M. Goodman

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja3122137 • Publication Date (Web): 22 Mar 2013

Understanding the Mechanism of the Asymmetric Propargylation of Aldehydes Promoted by BINOL-Derived Catalysts

Matthew N. Grayson and Jonathan M. Goodman*

Unilever Centre for Molecular Science Informatics, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom.

ABSTRACT:

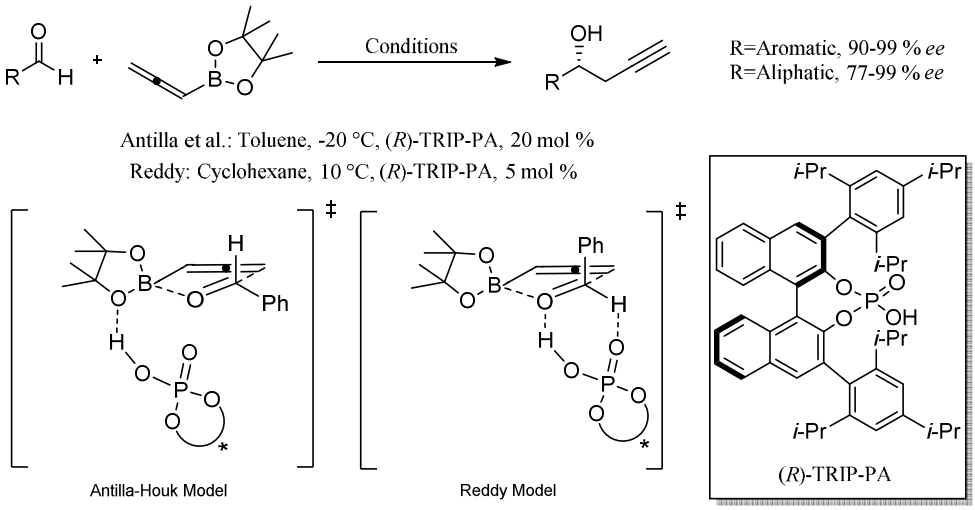
BINOL-derived phosphoric acids catalyze the asymmetric propargylation of aldehydes. DFT calculations showed that the reaction proceeds via a six-membered TS in which the catalyst Brønsted acidic site interacts with the pseudoaxial cyclic boronate oxygen and the phosphoryl oxygen interacts with the formyl proton. This model accurately predicts the stereochemical outcome observed experimentally. Replacement of the phosphoric acid hydroxyl group with an *N*-triflyl moiety has been included in the model by calculation, and a broader understanding achieved by qualitative assessment of similar reactions. We present a qualitative guide to rationalizing the experimental outcome and use this to make a prediction which was confirmed experimentally.

1. INTRODUCTION

Propargylation has become a key reaction for the construction of carbon-carbon bonds.[1-3] Propargylation of carbonyls, and the resulting homopropargylic alcohols, have been applied to the total synthesis of a wide range of natural products including zincophorin,[4] (-)-histrionicotoxin[5] and bafilomycin.[6] Whilst these versatile compounds are synthetically very useful, their preparation remains challenging relative to the synthesis of enantiomerically pure homoallylic alcohols. Selectivity issues can arise from propargylic reagent rearrangement to the allenic analogues to afford a mixture of the β-acetylenic and α-allenic carbinols.[7,8] Early asymmetric propargylation reactions made use of chiral allenyl reagents, notably those reported by Yamamoto,[9] Corey,[10] and Soderquist.[11] Recently, catalytic methods have emerged such as work by Denmark,[12] Yamamoto,[13] and Shibasaki.[14]

In 2012, Antilla et al. and Reddy independently reported the use of a chiral BINOL-derived phosphoric acid as an efficient catalyst for aldehyde propargylation (Scheme 1).[15,16] The reaction gives the corresponding homopropargylic alcohols in excellent yields and enantioselectivities for both aromatic and aliphatic aldehydes (Scheme 1), and employs an easily prepared allenylboronate which offers complete regioselective control.

Scheme 1 Asymmetric Propargylation of Aldehydes.[15,16]



However, the origins of enantioselectivity are unclear which would make the products of reactions involving novel substrates difficult to predict. Based on DFT calculations, Antilla et al. proposed that the reaction proceeds with protonation of the cyclic boronate pseudoequatorial oxygen by the chiral phosphoric acid and orientation of the phosphoryl oxygen towards the ortho-hydrogen of the equatorial phenyl group (Scheme 1). However, our previous work has indicated that single-point binding from the catalyst to the substrate cannot explain the observed enantioselectivity in similar reactions catalyzed by BINOL-derived phosphoric acids.[17-19] Reddy proposed that the catalyst hydroxyl group interacts with the aldehyde oxygen and the phosphoryl oxygen interacts with the aldehyde formyl proton (Scheme 1). However, this arrangement places the aldehyde phenyl group axial rather than equatorial, an arrangement found to be disfavored for aldehyde allylboration.[18]

Herein, we report the results of DFT calculations which provide mechanistic insight into this important propargylation reaction. Our calculations indicate that the reaction proceeds via a cyclic six-membered ring transition structure (TS) involving both a hydrogen bonding interaction from the catalyst hydroxyl group to the cyclic boronate pseudoaxial oxygen and an additional interaction from the catalyst phosphoryl oxygen to the aldehyde formyl proton. This mechanistic pathway is lower in energy than that proposed in the original papers and predicts the correct sense of enantioselectivity. We present a qualitative guide to rationalizing the experimental outcome which is consistent with the model derived from our study of aldehyde allylboration.[18]

2. COMPUTATIONAL DETAILS

The preferred reaction pathway for aldehyde propargylation was investigated using buta-1,3-diene-1,4-diol-phosphoric acid as a model for the catalyst,[19] implemented in Gaussian03 (Revision E.01),[20] using the B3LYP density functional,[21,22] and split-valence polarized 6-31G* basis set.[23,24] Single-point energies were taken using the M06-2X density functional,[25]

and the 6-31G* basis set using the Jaguar program (version 7.6).[26] These energies were used to correct the gas phase energies obtained from the B3LYP calculations.[27] All activation free energies are quoted relative to infinitely separated reagents.

To further validate the results obtained with the model system and to explore the origins of enantioselectivity, we also performed B3LYP/6-31G* calculations using the phosphoric acid derived from (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-phenol as a model,[15] implemented in Gaussian03 (Revision E.01).[20] This model was selected instead of the full catalyst to reduce computational time and to ensure results were directly comparable to those reported by Antilla et al. M06-2X/6-31G* single-point energy calculations were performed on the resulting structures using the Jaguar program (version 7.6),[26] and used to correct the gas phase energies.[27] All activation free energies are quoted relative to infinitely separated reagents.

Free energies in solution were derived from gas phase optimized structures (B3LYP/6-31G*) by means of a single-point calculation using M06-2X/6-31G* with the polarizable continuum model (PCM),[28] as implemented in the Jaguar program (version 7.6). These values were used to correct the Gibbs free energy derived from the B3LYP calculations.

3. RESULTS AND DISCUSSION

Investigation of uncatalyzed aldehyde propargylation identified 2 unique TSs with the benzaldehyde phenyl group either pseudoequatorial or pseudoaxial. The most favorable TS was found to be **TS-1**, with **TS-2** destabilized by the steric interaction between the cyclic boronate and the benzaldehyde phenyl group (Figure 1). The activation free energy of **TS-1** was calculated to be 32.9 kcal mol^{-1} when evaluated using B3LYP/6-31G*. The Gibbs free energy was corrected by taking a single-point energy using M06-2X/6-31G* which lowered the value of the activation free energy to 20.0 kcal mol^{-1}.

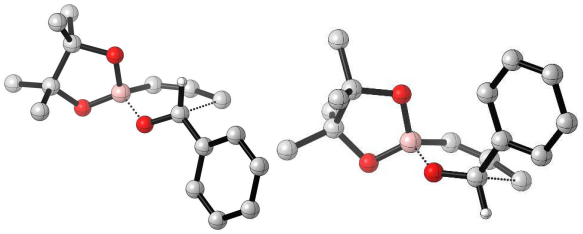


Figure 1 Competing TSs for the reaction of benzaldehyde and allenylboronic acid pinacol ester. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. Non-critical hydrogen atoms omitted for clarity.

Investigation of the catalyzed reaction using our model catalyst derived from buta-1,3-diene-1,4-diol-phosphoric acid, revealed the value of $\Delta G^{\ddagger}$ for the Antilla-Houk model (**TS-3**, Figure 2) to be approximately 5 kcal mol^{-1} lower in energy than the uncatalyzed activation barrier when evaluated using B3LYP/6-31G*. Alternative mechanisms include the Reddy model (**TS-4**), protonation of the aldehyde oxygen by the phosphoric acid (**TS-5**) and a ten-membered ring TS (**TS-6**). However, these mechanisms were found to be disfavored relative to **TS-3**. Interestingly, the aldehyde phenyl group in **TS-5** occupies the pseudoaxial position and was found to be lower in energy than the alternative pseudoequatorial TS. This is the result of increased steric interactions between the phosphoric acid and the phenyl group in the latter TS relative to TSs which involve protonation of the cyclic boronate pseudoequatorial oxygen in which there was a strong preference for the aldehyde substituent to be pseudoequatorial. This steric interaction can be avoided if the phenyl group is placed pseudoaxially.

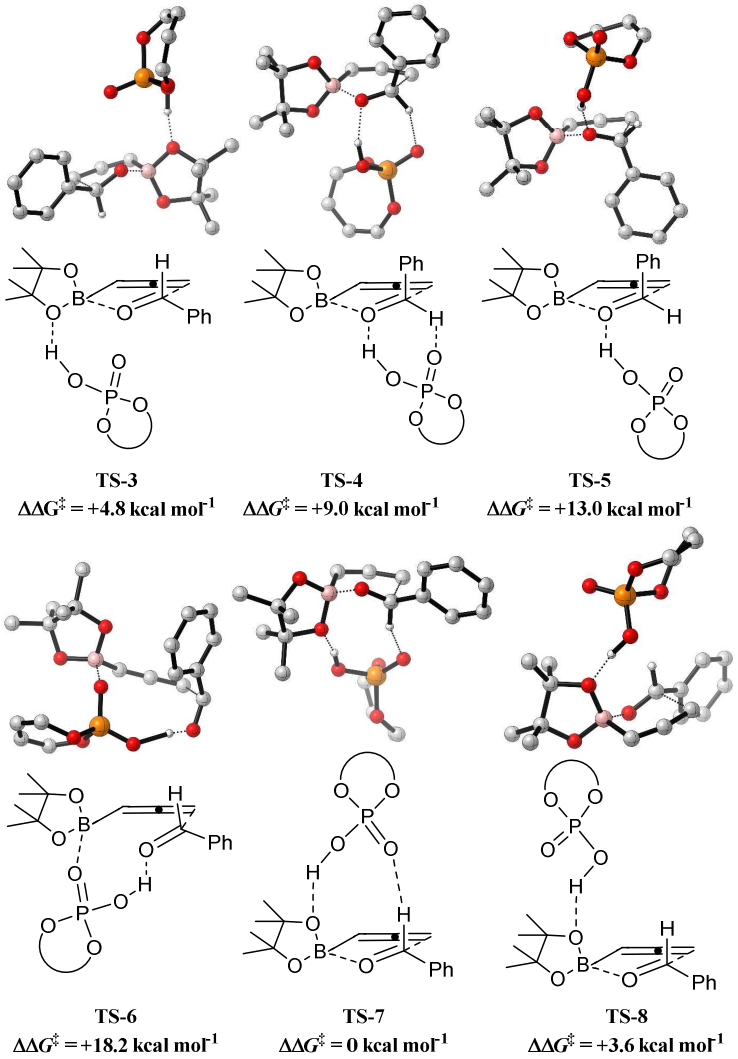


Figure 2 Competing TSs for the reaction of benzaldehyde and allenylboronic acid pinacol ester catalyzed by buta-1,3-diene-1,4-diol-phosphoric acid. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. Non-critical hydrogen atoms omitted for clarity.

Thorough exploration of the potential energy surface yielded a total of 64 unique TSs (see supporting information). The lowest energy TS was found to involve protonation of the cyclic boronate pseudoaxial oxygen by the phosphoric acid and a hydrogen bonding interaction between the phosphoryl oxygen and the formyl proton, a similar mechanism to our findings from the study of aldehyde allylboration (**TS-7**, Figure 2).[18] **TS-8** was found to involve protonation of the axial oxygen with no secondary interaction to the formyl proton, and was found to be disfavored relative to **TS-7**. Superposition of the 6 reacting ring atoms, axial oxygen and catalyst hydroxyl group of **TS-7** and **TS-8** allowed calculation of an RMSD value of 0.26 Å suggesting minimal geometric change between the 2 TSs. Therefore, the difference in energy between the two structures can be attributed to the enthalpic benefit of the formyl hydrogen bond. $\Delta E_{\text{M06-2X}}$ between the structures was found to be 3.6 kcal mol^{-1}, in close agreement with the value previously reported for the strength of the formyl hydrogen bond for aldehyde allylboration.[18]

The origins of enantioselectivity were investigated using (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-phenol as a catalyst model to ensure that our results were comparable to those reported by Antilla et al. Examination of the B3LYP free energies indicates that **TS-9*Re*** is the lowest energy TS which proceeds via protonation of the cyclic boronate pseudoaxial oxygen by the phosphoric acid with an additional stabilizing interaction to the aldehyde formyl proton from the phosphoryl oxygen (Figure 3). The free energy barrier for this pathway was found to be 5.5 kcal mol^{-1} lower than that corresponding to the background reaction, when evaluated at the B3LYP level of theory.

However, the B3LYP energies also indicated a flat potential energy surface with regard to the lowest *Si* TS. 3 TSs, all conformationally very different, were found to be separated by less than 0.7 kcal mol^{-1} (**TS-9*Si***, **TS-10*Si*** and **TS-11*Si***, Figure 3). These B3LYP studies weakly suggested the Antilla-Houk model to be the preferred pathway to the minor product. A clearer understanding of the potential energy surface would better allow rationalization of the enantioselective origins. The shortcomings of the B3LYP functional at describing TS energies have been well documented.[29-33] Whilst B3LYP has been found to give reliable TS geometries, the corresponding energies fail to accurately sum the many complex van der Waals interactions which lead to the overall catalytic effect. Therefore, M06-2X single-point energies should be taken, representing only a small additional calculation but providing a significant increase in precision when compared to experiments.[27] This new potential energy surface allowed a less ambiguous identification of the lowest energy *Si* TS (**TS-9*Si***). In **TS-9*Si***, the formyl hydrogen bond was found to be lengthened by 0.19 Å relative to **TS-12*Si***. This distortion serves to reduce the steric clash between the large catalyst aromatic substituent and the pinacol ester methyl groups. Despite this stabilization the pathway remains energetically disfavored, by 2.1 kcal mol^{-1}, relative to **TS-9*Re*.**

Therefore, the enantioselectivity can be rationalized using the formyl hydrogen bonded pathway. The computed enantioselectivity arising from **TS-9*Re*** and **TS-9*Si*** was found to be 97 % at 253 K, close to that seen experimentally. The origins of such strong selectivity for

the (*R*)-homopropargylic alcohol are due to the unfavorable steric clash between the pinacol ester methyl groups and the bulky catalyst aromatic group in **TS-9*Si***. This mechanistic understanding of aldehyde propargylation is consistent with our findings for aldehyde allylboration, both of which employ an M06-2X energy correction to compensate for the shortfalls of the B3LYP functional.

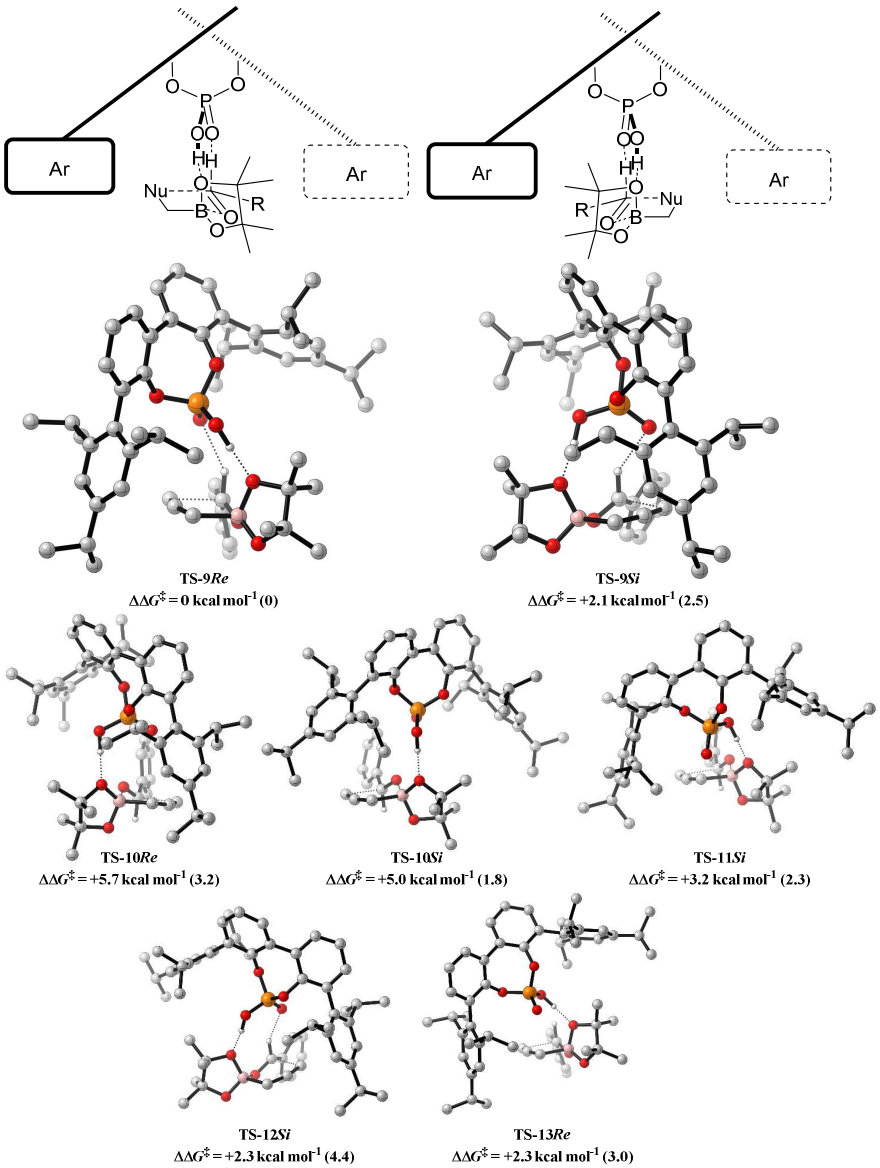


Figure 3 Competing TSs for the reaction of benzaldehyde and allenylboronic acid pinacol ester catalyzed by (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-phenol-phosphoric acid. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. B3LYP/6-31G* free energies in parentheses. Non-critical hydrogen atoms omitted for clarity.

TS-10*Re* and **TS-10*Si***, corresponding to the Antilla-Houk model, were found to be higher in energy than both **TS-9*Re***, **TS-9*Si*** and **TS-12*Si*** (Figure 3). Moreover, the predicted sense of enantioselectivity by this model is opposite to that observed experimentally. In **TS-10*Re***, the pinacol ester methyl groups must be placed in the sterically demanding pocket of the catalyst and whilst the absence of the formyl proton hydrogen bond means that this clash is reduced, **TS-10*Si*** still benefits from this less sterically demanding arrangement.

A total of 17 unique TS were located using this catalyst model (see supporting information), of which **TS-13*Re*** was found to be the lowest energy of the mono substrate-catalyst interaction model. To confirm that the results obtained using the biphenyl model accurately reflect the reaction conditions, **TS-9*Re*** and **TS-9*Si*** were optimized using the full catalyst system at the B3LYP/6-31G* level of theory (see supporting information). M06-2X/6-31G* single-point energy calculations were performed on the resulting structures and used to correct the B3LYP gas phase energies. The dihedral angle defined by both naphthyl groups (described by carbons 2,1,1' and 2', where 2 and 2' are the oxygen bearing carbons) in the new TSs was found to be 54.9° on average, in contrast to 43.2° in the biphenyl derived TSs. The relative free energies between the TSs increased by 0.6 kcal mol^{-1}. This indicates that the dihedral modification has a minor effect on the predicted selectivity and therefore confirms the validity of the biphenyl model catalyst.

Toluene (Antilla's conditions) and cyclohexane (Reddy's conditions) solvent effects were shown to have minimal impact on the relative free energies of the competing TSs due to their concerted and apolar nature, in full agreement with our findings for aldehyde allylboration.[18] Solvation of **TS-9*Re*** and **TS-9*Si*** led to an increase in relative free energy of just 0.4 kcal mol^{-1} in both solvents. The small size of these changes show that gas phase calculations are a reasonable approximation for aldehyde propargylation reaction conditions.

When the solvent was dichloromethane (DCM), however, the experiments show a drop in selectivity. Using the PCM method, solvation of **TS-9*Re*** and **TS-9*Si*** in DCM reduced the relative free energy from 2.1 to 1.0 kcal mol^{-1}, in agreement with the trend observed in the experimental data. **TS-9*Si*** has a weaker and longer formyl hydrogen bond than **TS-9*Re***, and this is one of the factors that favors *Re* attack over *Si* attack in non-polar solvents. In polar solvents, such as DCM, this favorable interaction stabilizing *Re* attack may be replaced by a favorable interaction between P=O and the polar solvent molecules for *Si* attack. In order to test this idea, complexes between DCM and buta-1,3-diene-1,4-diol-phosphoric acid were located and structures in which the P=O-solvent interaction was present and absent were compared. The free energy associated with this solvent-catalyst interaction was calculated to be 3.1 kcal mol^{-1}, which is comparable to the strength of the formyl hydrogen bond (see supporting information). A similar strength of interaction has been observed between the C=O of acetone and chloroform.[34] These calculations suggest that the lower enantioselectivity observed in polar solvents than non-polar solvents arises because the key formyl hydrogen bond is not strongly favored over interactions with polar solvent molecules.

To further test our mechanistic hypothesis, the effect of changing the catalyst was investigated. Experimentally, Antilla found that changing the 3 and 3' groups from 2,4,6-triisopropylphenyl to 3,5-bis(trifluoromethyl)phenyl reduced the *ee* from 74 % to 4 %. **TS-14*Re*** and **TS-14*Si*** were found to be closer in energy than **TS-9*Re*** and **TS-9*Si*** (Figure 4). This can be understood in terms of the reduced steric demands of the CF_3 groups relative to the isopropyl groups, resulting in lower levels of enantioselectivity. The lack of formyl hydrogen bond distortion in **TS-14*Si***, in contrast to **TS-9*Si***, is due to the absence of large sterically demanding 2,4,6-triisopropylphenyl groups. This absence allows maximum TS stabilization from the favorable formyl hydrogen bonding interaction.

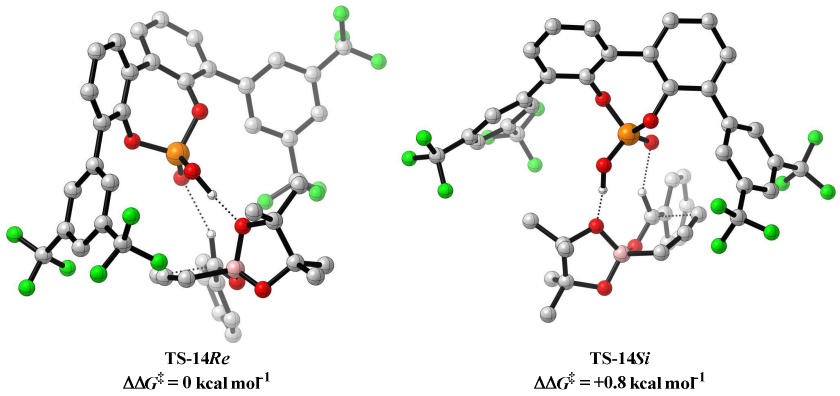


Figure 4 Competing TSs for the reaction of benzaldehyde and allenylboronic acid pinacol ester catalyzed by (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)phenyl)-1,1'-bi-2-phenol-phosphoric acid. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. Non-critical hydrogen atoms omitted for clarity.

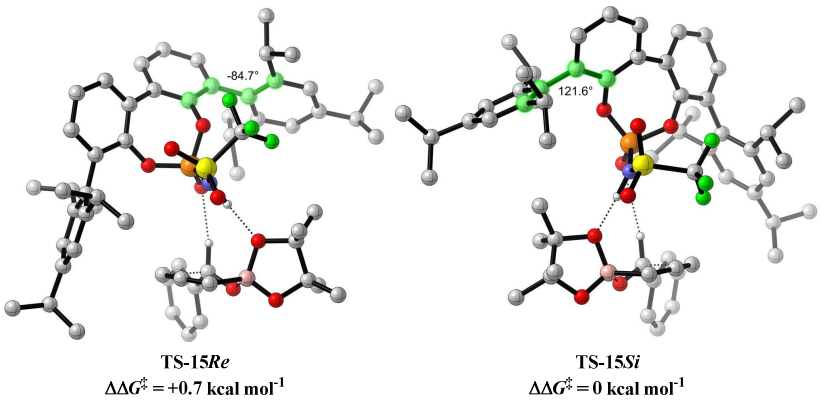


Figure 5 Competing TSs for the reaction of benzaldehyde and allenylboronic acid pinacol ester catalyzed by a BINOL-derived *N*-triflyl phosphoramide. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. Measured dihedrals highlighted in green. Non-critical hydrogen atoms omitted for clarity.

The use of a BINOL-derived *N*-triflyl phosphoramide bearing the same 3 and 3' groups as TRIP-PA resulted in a decrease in *ee* from 74 to 16 %, experimentally. This result was non-intuitive, given that the bulky aromatic substituents that usually control the enantioselectivity levels remained identical. 9 TSs were located for this reaction, of which **TS-15*Re*** and **TS-15*Si*** were the lowest in energy (Figure 5). Our calculations predict a dramatic fall in *ee* and suggest the reasons for this are the increased steric demands of the phosphoramide phosphorous centre relative to the phosphoric acid. To the best of our knowledge, this is the first report of mechanistic investigations into *N*-triflyl phosphoramides of this nautre.

The CF_3 group of the triflyl moiety was found to be preferentially orientated towards the less sterically demanding pocket of the catalyst, in a similar way to the pinacol ester methyl groups. This modifies the dihedral of the BINOL-derived scaffold and the aromatic substituent, towards which the CF_3 group is orientated, from 72.9° in **TS-9*Re*** to 84.7° in **TS-15*Re*** (Figure 5). The oxygens of the triflyl moiety also modify the dihedral of the substituent towards which they are orientated from 113.1° in **TS-9*Si*** to 121.6° in **TS-15*Si*** (Figure 5). Therefore, these catalyst backbone distortions create a larger cone of empty space around the protic hydrogen, reducing the impact of the pinacol ester methyl group clash with the catalyst 3 and 3' groups, lowering the energy of **TS-15*Si*** relative to **TS-15*Re***. This led to a lower *ee* relative to the reaction catalyzed by TRIP-PA. Furthermore, the pocket to the rear of the catalyst which accommodates the benzaldehyde phenyl group in the *Re* TS becomes more sterically demanding, because of the CF_3 distortion, than in the corresponding TRIP-PA TS. However, in the *Si* TS, this pocket only accommodates the allenylboronate hydrogens and so is less destabilized than the *Re* TS.

This implies that if the strong steric demands of the substrate are bound to the catalyst Brønsted acidic moiety, the *ee* should be higher in a reaction catalyzed by the phosphoric acid than by the phosphoramide, providing both are effective catalysts for the reaction. Therefore, in examples where the phosphoramide gives high *ee*, it is expected that the sterically demanding substrate is bound to the phosphoryl oxygen. Table 1 contains examples in which the general trend outlined above is observed. Without detailed mechanistic investigation, only a correlation can be established. However, combining these data with the results of our calculations, supported the hypothesis.

Table 1 Examples of reactions catalzyed by chiral phosphoric acids and *N*-triflyl phosphoramides.

Reaction	Mode of Activation	Strong Steric Demands	*ee* with PA / %	*ee* with *N*-triflyl phosphoramide / %
Indole 1,4-additon[35]	Asymmetric Nuc. at P=O	P=O	-	80-92 (10 examples)
Friedel-Crafts Alkylation[36]	Asymmetric Nuc. at P=O	P=O	-	84-94 (7 examples)
Propargylation of Aldehydes[15]	Asymmetric Nuc. at Brønsted Acidic Site	Brønsted Acidic Site	74	16
Asymmetric Reduction of Ketones[37]	Symmetric Nuc. at P=O	Brønsted Acidic Site	46	-17
Reductive Amination[38]	Symmetric Nuc. at P=O	Brønsted Acidic Site	91 89	26 30

An additional test of the model was performed by investigating the effects of aldehyde substitution upon *ee*. The aldehyde that gave the lowest *ee* under the optimized conditions was cyclohexanecarboxaldehyde. TSs were located based around the formyl proton hydrogen bonding model (**TS-16*Re*** and **TS-16*Si***, Figure 6) which show a reduction in the relative free energy between *Re* and *Si* compared to **TS-9*Re*** and **TS-9*Si***, in agreement with experimental results. The cyclohexyl substituent involves more severe clashing with the bulky aromatic group at the rear of the catalyst than in the case of the flat benzaldehyde phenyl group in the *Re* TS. In the case of the *Si* TS, the aldehyde substituent occupies the empty pocket and so is stabilized relative to the *Re* TS. Whilst this effect lowers the *ee* observed experimentally, the overall sense of enantioselectivity is determined by the unfavorable interactions between the pinacol ester methyl groups and the bulky catalyst aromatic substituent.

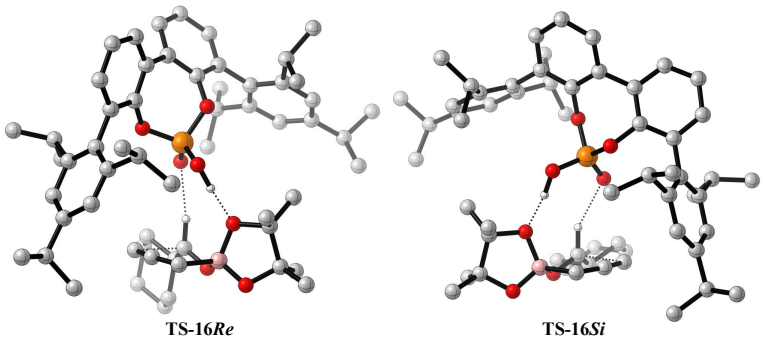


Figure 6 Competing TSs for the reaction of cyclohexanecarboxaldehyde and allenylboronic acid pinacol ester catalyzed by (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-bi-2-phenol-phosphoric acid. Geometries B3LYP/6-31G*, single-point energies M06-2X/6-31G*. Non-critical hydrogen atoms omitted for clarity.

Experimental test of the model

To assess the utility of our qualitative model we hypothesised that the combination of cyclohexanecarboxaldehyde and the BINOL-derived *N*-triflyl phosphoramide described above could lead to a large reduction in *ee* for this reaction. The modified catalyst creates a larger cone of empty space about the protic hydrogen bond and therefore reduces the effect of the pinacol ester methyl groups. This, in combination with the sterically demanding cyclohexanecarboxaldehyde which prefers to be placed in the empty pocket to the rear of the catalyst, should lead to a reduction in the energetic preference for the *Re* TS.

To test this prediction, firstly the *N*-triflyl phosphoramide (**1**) was synthesised (see supporting information). The reaction of allenylboronic acid pinacol ester and cyclohexanecarboxaldehyde was then conducted in the presence of **1** under the same conditions described by Antilla et al. (Figure 7). The product displayed the same sense of optical rotation as that reported in the original paper when catalyzed by (*R*)-TRIP-PA. The absolute stereochemistry and *ee* were determined by analysis of both diastereomeric Mosher esters (see supporting information). The results showed the product formed was the (*R*)-enantiomer in 39 % *ee*. This illustrated that by understanding the qualitative model presented here, experimental predictions can be made without the need for further calculations and demonstrated its power for application in the design of asymmetric methodology.

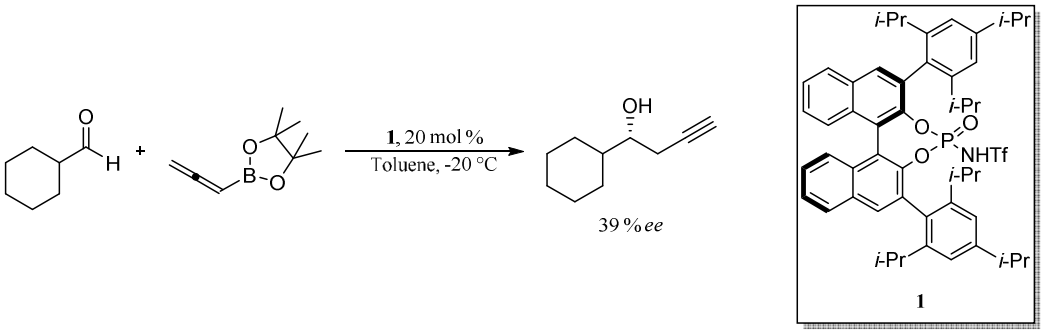


Figure 7 Reaction of cyclohexanecarboxaldehyde and allenylboronic acid pinacol ester catalyzed by **1**.

CONCLUDING REMARKS

In conclusion, DFT calculations have suggested that asymmetric aldehyde propargylation proceeds via a six-membered TS in which the catalyst Brønsted acidic site interacts with the cyclic boronate pseudoaxial oxygen and the phosphoryl oxygen interacts with the formyl proton. This mode of activation is energetically preferred to the models proposed in the original papers.[15,16] This model accurately predicts the experimental stereochemical outcome and reproduces the observed trends in enantioselectivity when the aldehyde substituent is changed, allowing approximate trends in *ee* to be determined for novel substrates. We present

a qualitative guide to rationalizing the experimental outcome (Figure 3) that is consistent with the results from our study of aldehyde allylboration which demonstrates the generality of this reaction model.[18]

Furthermore, replacement of the phosphoric acid hydroxyl group with an *N*-triflyl moiety has been included in the model by calculation, and a broader understanding achieved by qualitative assessment of similar reactions. This exchange leads to an erosion of the reaction *ee* when highly sterically demanding groups bind to the OH/NH site. The opposite is true, leading to higher *ee*, when the sterically demanding groups occupy the phosphoryl pocket of the catalyst. This qualitative guide was used to make a prediction which was confirmed experimentally.

The model presented here for aldehyde propargylation gives a clear mechanistic insight into this reaction and should serve to promote further development of synthetic methodology involving this mode of activation.

ASSOCIATED CONTENT

Supporting Information. 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; full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author
jmg11@cam.ac.uk

ACKNOWLEDGMENT

We thank the EPSRC for funding and Unilever.

REFERENCES

(1) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Edit.* **1996**, *34*, 2589.
(2) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914.
(3) Ljungdahl, N.; Kann, N. *Angew. Chem. Int. Edit.* **2009**, *48*, 642.
(4) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701.
(5) Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 4446.
(6) Marshall, J. A.; Adams, N. D. *Org. Lett.* **2000**, *2*, 2897.
(7) Wotiz, J. H. *J. Am. Chem. Soc.* **1950**, *72*, 1639.
(8) Favre, E.; Gaudemar, M. *J. Organomet. Chem.* **1975**, *92*, 17.
(9) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.
(10) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc.* **1990**, *112*, 878.
(11) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799.

(12) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.
(13) Usanov, D. L.; Yamamoto, H. *Angew. Chem. Int. Edit.* **2010**, *49*, 8169.
(14) Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638.
(15) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem. Int. Edit.* **2012**, *51*, 1391.
(16) Reddy, L. R. *Org. Lett.* **2012**, *14*, 1142.
(17) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.
(18) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716.
(19) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 4070.
(20) Frisch, M. J.; et al., *Gaussian 03;* Gaussian, Inc., Wallingford CT, 2004.
(21) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
(22) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(23) Krishnan R.; Binkley J. S.; Seeger R.; Pople J. A. *J. Chem. Phys.* **1980**, *72*, 650.
(24) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1992**, *197*, 499.
(25) Zhao, Y.; Truhlar, D. *Theor. Chem. Acc.* **2008**, *120*, 215.
(26) Jaguar, version 7.6, Schrodinger, LLC, New York, NY, 2009.
(27) Simón, L.; Goodman, J. M. *Org. Biomol. Chem.* **2011**, *9*, 689.
(28) Mennucci B.; Tomasi J. *J. Chem. Phys.* **1997**, *106*, 5151.
(29) Zhao, Y.; Truhlar, D. G. *Org. Lett.* **2006**, *8*, 5753.
(30) Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. v. R. *Org. Lett.* **2006**, *8*, 3631.
(31) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364.
(32) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 10478.
(33) Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749.
(34) Singh, S.; Murthy, A. S. N.; Rao, C. N. R. *Trans. Faraday Soc.* **1966**, *62*, 1056.
(35) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem. Int. Edit.* **2008**, *47*, 593.
(36) Wang, S.-G.; Han, L.; Zeng, M.; Sun, F.-L.; Zhang, W.; You, S.-L. *Org. Biomol. Chem.* **2012**, *10*, 3202.
(37) Zhang, Z.; Jain, P.; Antilla, J. C. *Angew. Chem. Int. Edit.* **2011**, *50*, 10961.
(38) Enders, D.; Liebich, J. X.; Raabe, G. *Chem-Eur. J.* **2010**, *16*, 9763.

Table of Contents Graphic: