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A Hydrogen Bond Rationale for the Enantioselective β-Alkenylboration of Enones Catalyzed by *O*-Monoacyltartaric Acids

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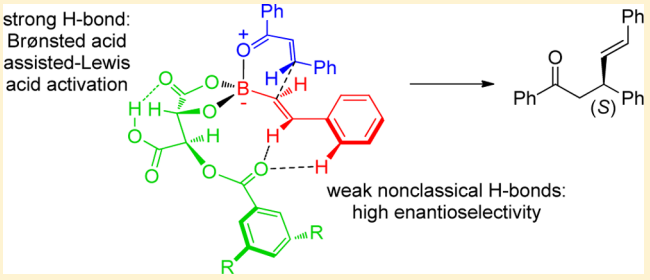
Supporting Information

ABSTRACT: DFT calculations suggest that *O*-monoacyl L-tartaric acids catalyze the asymmetric conjugate alkenylboration of enones through transition structures that are stabilized by hydrogen-bonding interactions. Formation of a five-membered acyloxyborane is proposed. The hydrogen of the free carboxy group derived from the catalyst interacts with the carbonyl group of the cyclic acyloxyborane, stabilizing the transition structure and reducing the flexibility of the system. Additional stabilizing nonclassical CH···O hydrogen-bond interactions seem to determine the observed enantioselectivity.

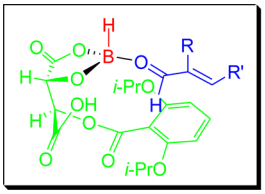


In 2010, Sugiura and co-workers reported that *O*-monoacyl L-tartaric acids (**1**) organocatalyze the conjugate alkenylboration of enones with high yields and enantioselectivities.[1] Within the acyl groups tested, the 3,5-di-*tert*-butylbenzoyl group gave optimized yields and enantioselectivities. As an example, the conjugate addition of (*E*)-styrylboronic acid (**3**) to chalcone (**2**) with 10 mol % of (2*R*,3*R*)-2-*O*-(3,5-di-*tert*-butylbenzoyl)-tartaric acid (**1a**) in toluene at 50 °C for 24 h gave the desired product **4** in 92% yield with 87% ee (Scheme 1).

To our knowledge, that report demonstrated for the first time that α-hydroxy acids could be used as organocatalysts in organoboron reactions.[2] More recently, tartaric acid has also been described to organocatalyze the enantioselective addition of alkenylboronic esters to *N*-acylquinoliniums.[3] Given that boronic acids have long been known to selectively bind to diols and α-hydroxy acids,[4,5] it is surprising that such interactions have not been exploited in the field of organocatalysis earlier. In contrast, several reports on the conjugate alkenylborations accelerated by chiral biphenols,[6] a resin-supported peptide,[7] and trifluoroacetic anhydride[8] have appeared in the literature.

In a related but conceptually different approach, Yamamoto and co-workers used *O*-monoacyltartaric acids to stoichiometrically prepare chiral acyloxyboranes (CAB), which as a class of Lewis acid can catalyze different asymmetric reactions efficiently.[9] NOE studies for CAB-complexed methacrolein and crotonaldehyde suggested that facial differentiation originated from π-stacking between the enal and the aromatic ring of the acyl group.[9d]

On the basis of such premises and our previous theoretical studies for similar reactions,[10] we propose that the reaction of boronic acid **3** with catalyst **1** would initially give rise to the formation of chiral intermediate **5** (Scheme 2). The electron-withdrawing acyloxy group in **5** would enhance the electrophilicity of the boron atom to facilitate coordination to the carbonyl oxygen of enone **2**. Intramolecular attack of the carbon attached to the boron atom to the *Re* face of the activated enone in the highly ordered complex **2**−**5** would then give rise to the addition product with the *S* absolute configuration at the β carbon. The chiral catalyst would be released by ligand exchange, while protonation would yield β-alkenyl ketone **4**.



Yamamoto's model: CAB-complexed methacrolein (R = Me, R' = H) and crotonaldehyde (R = H, R' = Me)

To shed light into the mechanism of catalysis of *O*-monoacyltartaric acids in the enantioselective conjugate addition of alkenylboronic acids to enones we performed a theoretical study using DFT methods as implemented in Gaussian 09, revision D.01.[11] We have used the smallest catalyst tartaric acid **1b** (R = Me, Scheme 1) to reduce the number of atoms. We have analyzed possible competitive pathways for the conjugate addition since many different boron species could be formed by ligand exchange due to the presence of multiple free hydroxy and carboxy groups in the catalyst and the methanol additive (see the Supporting Information). We performed thorough conformational searches for all the studied structures, analyzed the features of the reactants and the transition structures (TSs), and compared the energetics of all the possible pathways to identify the origin of the

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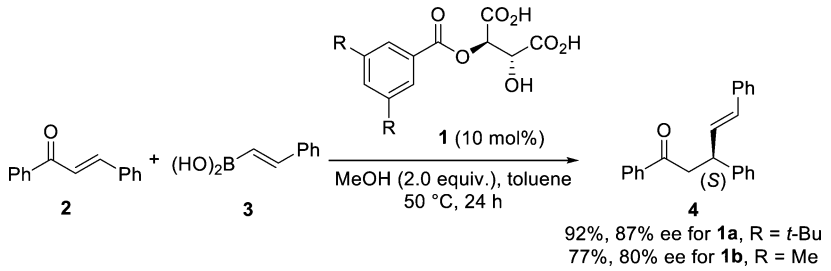
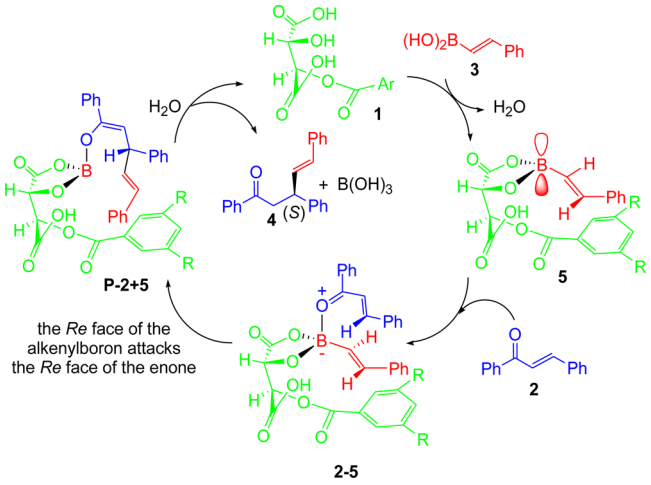
Scheme 1. Enantioselective Conjugate Addition of (*E*)-Styrylboronic Acid to Chalcone Catalyzed by *O*-Monoacyltartaric Acids



Scheme 2. Possible Catalytic Cycle



experimentally observed catalytic activity and enantioselectivity. Energies and geometries shown herein correspond to structures optimized at the B3LYP/6-311+G** level of theory.[12]

Examination of the FMOs of the reagents gives a very similar picture to the one found for the BINOL-catalyzed conjugate alkenylboration.[10b] Chalcone (**2**) and (*E*)-styrylboronic acid (**3**) show a typical dominant interaction for a nucleophilic addition, i.e., that between the LUMO of the enone and the HOMO of the alkenylboronic acid (energy gap 4.06 eV) (Figure 1).[13] Intermediate **5** has lower energy FMOs so it is less nucleophilic and more electrophilic showing very similar $HOMO_5$–$LUMO_2$ and $HOMO_2$–$LUMO_5$ energy gaps (4.35 and 4.36 eV, respectively). However, the later interaction leads to a tightly bound complex **2**–**5** (d_{B-O} 1.64 Å) with a small intramolecular HOMO–LUMO gap of 2.47 eV, so even if a very small amount of the complex is formed it should undergo conjugate addition promptly.[14] We were not able to locate either molecular or coordination complexes for (*E*)-styrylboronic acid (**3**) with **2**. Contrary to the mode of activation of BINOLs, where the higher electrophilicity of boron originated from the twisted geometry of the derived cyclic boronate and the resulting poorer ability of the oxygens to donate electron density into the vacant p orbital of the boron atom, we propose that the enhanced Lewis acidity of borolane **5** can be attributed to the presence of the electron-attracting acyloxy group in the ring. This is corroborated by the coefficients of the carbonyl atoms in the LUMO of **5** (ca. 0.10).

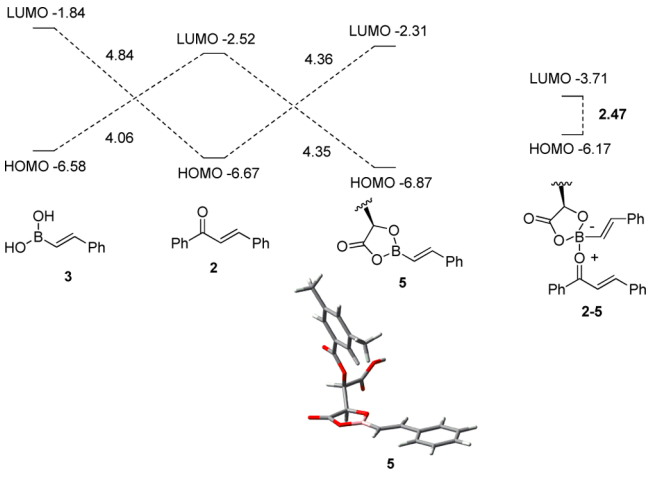


Figure 1. Correlation diagrams (B3LYP/6-311+G** energies in eV) and optimized geometry of intermediate **5**.

Location of the transition structures for the conjugate addition reactions provided further evidence for the hypothesis of Lewis acid activation of the enone via formation of complex **2**–**5** and also suggested that other interactions contribute to accelerate the reaction. Although the reaction of (*E*)-styrylboronic acid (**3**) with catalyst **1b** to give intermediate acyloxyborane **5** appears to be slightly exergonic (ΔG = −0.09 kcal/mol), the free activation energy for the conjugate alkenylboration was calculated to be much lower than for the noncatalyzed reaction, as well as for those for the methanol hemiester and ester derivatives (Figure 2).[15] The energy barriers corresponding to the transition structures for the catalyzed reaction were ca. 10 kcal/mol lower than those for the background reaction.

Figure 3 gathers the minimum energy geometries for the transition structures of the reactions of chalcone with (*E*)-styrylboronic acid (**3**) and chiral borolane **5**.[16] It is important to remark that for the achiral boron compounds such as (*E*)-

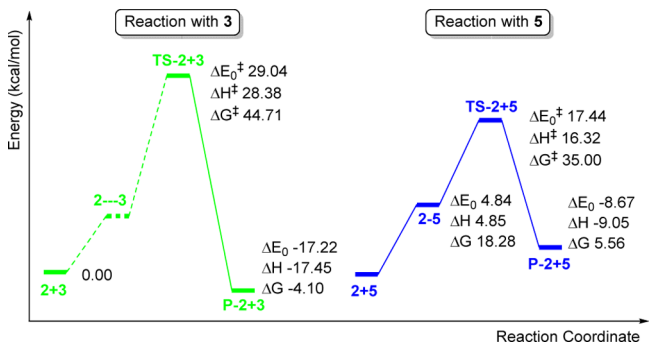


Figure 2. Reaction coordinates for the lower energy TSs corresponding to the alkenylboration of chalcone (**2**) with (*E*)-styrylboronic acid (**3**) and chiral borolane **5**, with B3LYP/6-311+G** energies from separate reactants in kcal/mol.

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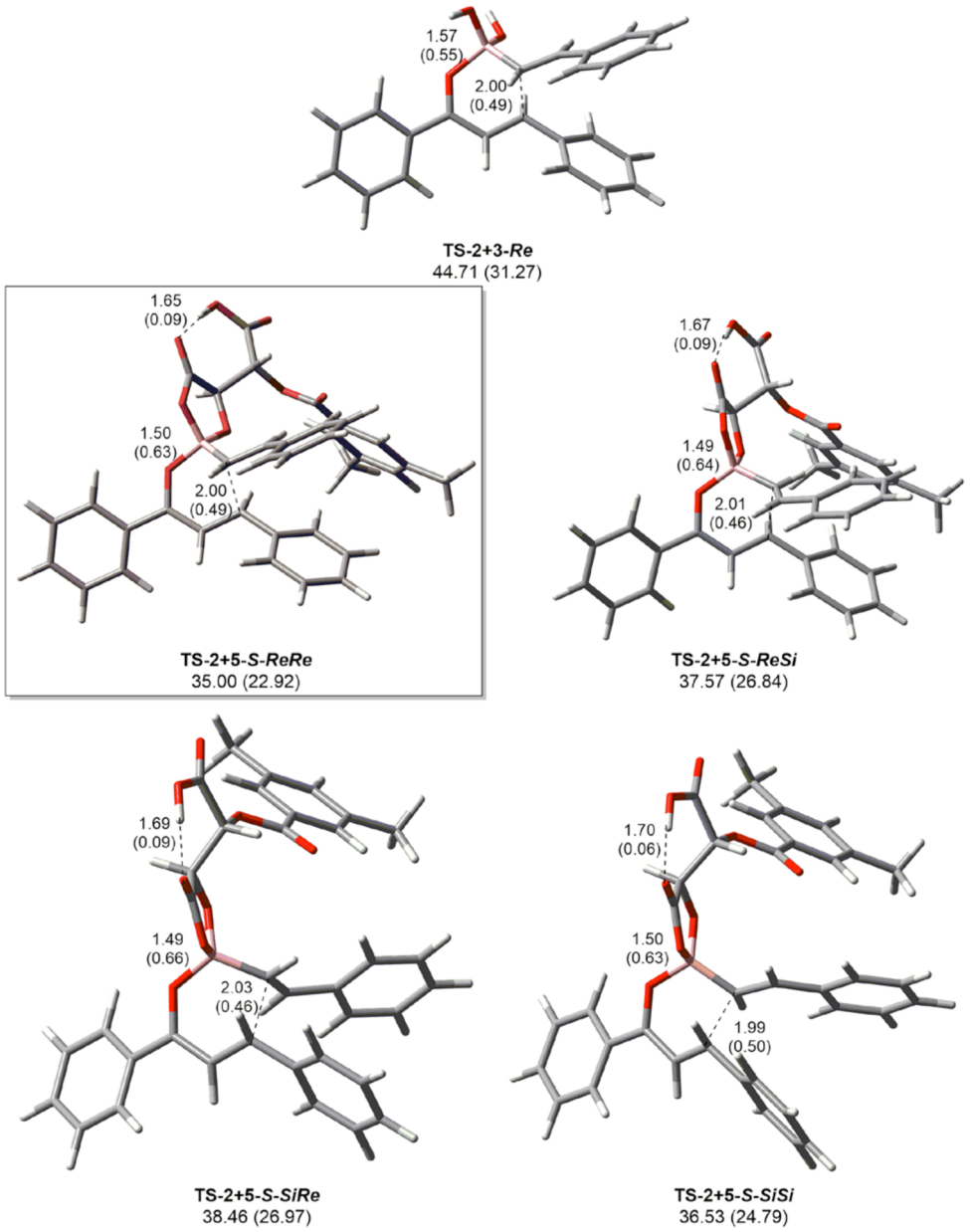

Figure 3. B3LYP/6-311+G**-optimized geometries of selected TSs for the alkenylboration reactions of chalcone (**2**) with (*E*)-styrylboronic acid (**3**) and chiral borolane **5** with interatomic distances in angstroms and, in parentheses, Wiberg bond indexes. Free activation energies in the gas phase and in toluene, in parentheses, from separate reactants in kcal/mol.

styrylboronic (**3**) there are two possible approaches depending on the face to the alkenylboron being exposed (*Re* or *Si*), which lead to different conformations of the same product. In the case of chiral intermediate **5** the situation is more complex. Both lobes of the vacant p orbital of the boron atom in **5** can interact with the enone oxygen during coordination, so two diastereomeric complexes with either the *R* and *S* configuration at the sp^3 boron stereogenic center can be obtained. We have found that structures in which the boron atom has the *S* absolute configuration are more stable.

All the transition structures exhibit six-membered sofa-like geometries with C−C distances in the range 1.96−2.06 Å and B−O within 1.48−1.58 Å. Interestingly, in the transition structures for chiral borolane intermediate **5**, the hydrogen of the free carboxy group derived from the catalyst interacts with the carbonyl oxygen of the cyclic acycloxyborane (H···O distances ca. 1.7 Å).[17] These strong intramolecular hydrogen-bonding interactions stabilize the transition structures by 23.4 kcal/mol and lock the conformation of the system.[18] It is interesting to note that such type of interactions are not observed in intermediate **5**, therefore we propose that they are originated to stabilize the charge formed during the course of the reaction, thus mimicking enzymatic catalysis mechanisms.[19] Hydrogen-bonding interactions become stronger as the charge is reorganized in going from separate reactants to the transition state. The optimized geometry of the complex **2+5-*S*-*ReRe*** is shown in Figure 4, together with another view of the corresponding TS. The B−O distance and the strength of the hydrogen bond in the complex are nearly the same as those for the TS. We postulate that the hydrogen bond between the free carboxy group derived from the catalyst and the carbonyl of the cyclic acyloxyborane is responsible for the catalyst activity. This

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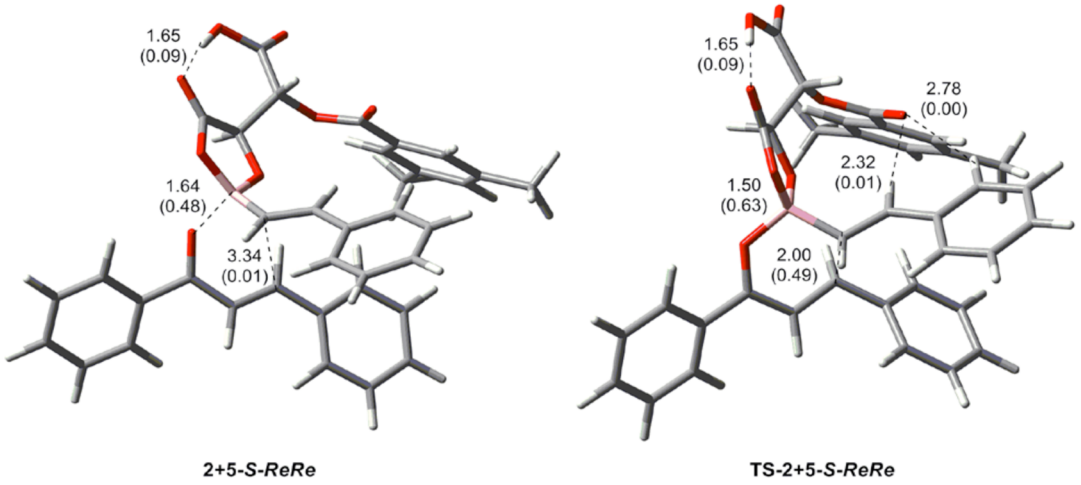

Figure 4. Optimized geometries of the complex and TS of the most favorable pathway for the alkenylboration reaction of chalcone with chiral borolane **5** with interatomic distances in Å and, in parentheses, Wiberg bond indexes.

could be classified as a special case of intramolecular Brønsted acid assisted Lewis acid catalysis (BLA), as defined by Yamamoto.[20] Calculations correctly predict the *S* absolute configuration of the product and estimate the enantiomeric excess for the reaction of **1b** (ee experimental 80%, computed 82%). The most favorable attack, corresponding to the approach of the *Re* face of **5** to the *Re* face of enone **2** (**TS-2+5-*S*-*ReRe***), is 1.5 kcal/mol lower in energy than the closest transition structure (**TS-2+5-*S*-*SiSi***). In analogy to the work of Yamamoto and co-workers on enantioselective reactions of chiral acyloxyboranes, we anticipated that π-stacking interactions between the aromatic ring of the acyl group and the alkenyl moiety would dictate the facial differentiation. However, we were not able to locate any conformations for the transition structures that presented such type of interactions, possibly due to geometry constraints of the highly compact system under study. Instead, we propose that transient nonclassical C(sp^2)−H···O hydrogen-bond interactions between the carbonyl oxygen of the acyl substituent and two hydrogens of the alkenyl group determine the observed enantioselectivity (Figure 4).[21] NBO calculations indicated that such interactions should stabilize **TS-2+5-*S*-*ReRe*** by over 1.0 kcal/mol, which is close to the energy difference with the most stable transition structure corresponding to the attack of the *Si* face of the enone (**TS-2+5-*S*-*SiSi***). The geometry of the latter prevents the formation of these key stabilizing hydrogen-bond interactions since the acyl moiety and the alkenyl groups are too far away. CH···O NCHBs in the other transition structure corresponding to attack of the *Re* face of the enone (**TS-2+5-*S*-*ReSi***), though present, are weaker (ca. 0.3 kcal/mol, 2.65 Å). In addition, **TS-2+5-*S*-*ReSi*** is also more sterically congested than **TS-2+5-*S*-*ReRe***, and a clash between two hydrogens belonging to the alkenyl moiety (H−H distance 2.09 Å) is observed.

In conclusion, the results of the theoretical study presented herein provided some insight on the mechanism of the asymmetric alkenylboration of enones catalyzed by chiral *O*-monoacyltartaric acids. We postulate that the formation of a strong intramolecular hydrogen bond between the hydrogen of the free carboxy group derived from the catalyst and the carbonyl oxygen of the cyclic acyloxyborane along the course of the reaction is responsible for the catalytic activity observed experimentally. In addition, owing to such interactions the system becomes rigid. A second type of hydrogen-bond interactions, namely the nonclassical C(sp^2)−H···O hydrogen-bond interactions between the carbonyl oxygen of the acyl substituent and two hydrogens of the alkenyl group, account for the high levels of enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra in $CDCl_3$ to study the formation of acyloxyborane **5**; computational methods with full list of authors in the Gaussian 09 reference; shapes and energies of FMOs of reactants; optimized geometries of structures not included in the paper; Cartesian coordinates, energies, and number of imaginary frequencies of all stationary points. 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.

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■ REFERENCES

(1) Sugiura, M.; Tokudomi, M.; Nakajima, M. *Chem. Commun.* **2010**, *46*, 7799−7800.
(2) Our groups have been working independently on this subject in recent years . Grimblat, N.; Sarotti, A. M.; Pisano, P. L.; Pellegrinet, S. C. Unpublished results.
(3) Kodama, T.; Moquist, P. N.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 6316−6319.
(4) For binding studies, see: (a) Kustin, K.; Pizer, R. *J. Am. Chem. Soc.* **1969**, *91*, 317−322. (b) Friedman, S.; Pace, B.; Pizer, R. *J. Am. Chem. Soc.* **1974**, *96*, 5381−5384. (c) Babcock, L.; Pizer, R. *Inorg. Chem.* **1980**, *19*, 56−61. (d) Pizer, R.; Ricatto, P. J. *Inorg. Chem.* **1994**, *33*, 2402−2406. (e) Bromba, C.; Carrie, P.; Chui, J. K. W.; Fyles, T. M. *Supramol. Chem.* **2009**, *21*, 81−88.
(5) For recent applications, see: (a) Gray, C. W.; Houston, T. A. *J. Org. Chem.* **2002**, *67*, 5426−5428. (b) Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676−3677. (c) Xu, W.-Z.; Huang, Z.-T.;

Zheng, Q.-Y. *Tet. Letters* **2008**, *49*, 4918−4921. (d) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd completely revised ed.; Wiley-VCH: Weinheim, 2011. (e) Wu, Y.; Guo, H.; James, T. D.; Zhao, J. *J. Org. Chem.* **2011**, *76*, 5685−5695. (f) Chaudhari, S. R.; Suryaprakash, N. *J. Org. Chem.* **2012**, *77*, 648−651.

(6) Chiral biphenols efficiently catalyze the enantioselective addition of boronic acids to carbonyl compounds, imines and iminium ions. For references on conjugate alkenylborations, see: (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908−4909. (b) Lundy, B. J.; Jansone-Popova, S.; May, J. A. *Org. Lett.* **2011**, *13*, 4958−4961. (c) Le, P. Q.; Nguyen, T. S.; May, J. a. *Org. Lett.* **2012**, *14*, 6104−6107. (d) Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965−19968.

(7) For a resin-supported peptide-catalyzed conjugate addition of alkenylboronic acids to a γ-hydroxy-α,β-unsaturated aldehyde, see: Akagawa, K.; Sugiyama, M.; Kudo, K. *Org. Biomol. Chem.* **2012**, *10*, 4839−4843.

(8) For trifluoroacetic anhydride promoted/catalyzed conjugate alkenylborations of enones, see: (a) Roscales, S.; Csáky, A. G. *Org. Lett.* **2012**, *14*, 1187−1189. (b) Roscales, S.; Rincón, Á.; Buxaderas, E.; Csákÿ, A. G. *Tetrahedron Lett.* **2012**, *53*, 4721−4724.

(9) For leading references, see: (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254−6255. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481−1483. (c) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041−1042. (d) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412−10413. (e) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917−6919. (f) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495.

(10) (a) Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3116−3117. (b) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *J. Org. Chem.* **2008**, *73*, 5078−5089.

(11) Frisch, M. J.; et al. Gaussian 09; Gaussian, Inc., Wallingford, CT, 2013.

(12) Initially, we used the B3LYP/6-31G* method, but the enantioselectivity was overestimated (ee experimental 80%, computed 98%). Therefore, we decided to reoptimize the most stable conformers for all studied species at the B3LYP/6-311+G** level of theory. This bigger basis set adds polarization functions for hydrogens and diffuse functions for heavy atoms (B, C, and O in our case), which would give a better estimate of the total energy of the systems and, ultimately, allow us to reproduce the enantioselectivity and better understand the origin of the experimental results. B3LYP/6-311+G**-optimized geometries were very similar to their B3LYP/6-31G* counterparts. However, gas-phase free energy barriers increased ∼4−6 kcal/mol, and as a result, the free energy difference between the background and the catalyzed reactions decreased, while the computed ee fit the experimental value.

(13) The methanol-derived hemiester and ester exhibit a similar behavior to the boronic acid but are slightly more nucleophilic ($HOMO_{alkenylboron}$−$LUMO_2$ 3.88 and 3.83 eV, respectively).

(14) Complex **2**−**5** was located through intrinsic reaction coordinate (IRC) calculations followed by full geometry optimization.

(15) The association of the reactants in an early stage of the reaction to form of coordination complex **2**−**5**, though computed to be quite demanding mainly due to entropy reasons, allows the breakdown of the free energy barrier in two energy-feasible steps: complexation and conjugate addition: Domingo, L. R.; Aurell, M. J.; Arnó, M.; Sáez, J. A. *J. Org. Chem.* **2007**, *72*, 4220−4227.

(16) Transition structures were named as follows: TS followed by the numbers corresponding to the reactants, then the absolute configuration of the boron atom (when necessary) and finally the faces of the enone (when necessary) and the alkenylboronate being exposed. For example, the lowest energy TS **TS-2+5-*S*-*ReRe*** corresponds to the TS originated from reaction between enone **2** and acyloxyborane **5** via the complex with the *S* configuration at boron and attack the *Re* faces of the enone and the alkenylboronate. Such TS gives rise to the observed (*S*)-enantiomer.

(17) We analyzed the possibility that the hydrogen of the free carboxy group coordinated to any of the other oxygens present in the studied system by manually preparing all possible input structures. However, the resulting optimized geometries had much higher energies than the ones shown herein, suggesting than the carbonyl is the more reactive site for hydrogen bonding.

(18) Corresponding to second-order interaction energies obtained from NBO analysis.

(19) (a) Shan, S.-O.; Herschlag, D. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14474−14479. (b) Kim, K. S.; Oh, K. S.; Lee, J. Y. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 6373−6378.

(20) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924−1942.

(21) Several non-classical CH···O hydrogen bonds (NCHBs) have been proposed to induce high levels of stereoselectivity in many organic transformations. $C(sp^2)$−H···O hydrogen bonds were reported to have $\Delta H \sim 0.9$ kcal/mol and H−O distances ∼ 2.38 Å. For a recent review, see: Johnston, R. C.; Cheong, P. H.-Y. *Org. Biomol. Chem.* **2013**, *11*, 5057−5064.