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Authors: Sebastián O. Simonetti and Silvina Pellegrinet

Asymmetric Organocatalytic C-C Bond Forming Reactions with Organoboron Compounds: A Mechanistic Survey

Sebastián O. Simonetti,[a] and Silvina C. Pellegrinet*[a]

Dedicated to the memory of Prof. Dr. Edmundo A. Rúveda

Abstract: The recent development of asymmetric organocatalytic C-C bond forming reactions involving organoboranes has attracted big interest in the synthetic community. Asymmetric organocatalytic additions to enones, aldehydes, ketones, imines, dienes and related systems can be carried out with different organoboron compounds (boronic acids and esters and trifluoroborate salts) to give products with very good yields and enantiomeric ratios. In particular, many BINOL and α-hydroxyacid derivatives have been used as chiral organocatalysts. In this review, we describe the mechanisms that have been proposed based on theoretical and experimental studies for asymmetric organocatalytic C-C bond forming reactions with organoboron compounds. The mechanistic understanding that has been gained should contribute to the progress of this promising area of organic chemistry.

1. Introduction

Organoboron compounds exhibit wide synthetic versatility and availability.[1,2] The hydroboration reaction developed by Brown[3] demonstrated the potential of organoboranes, providing an invaluable tool to inspire the development of further reactions.[4] Boranes played a key role in the progress of many areas of modern organic chemistry.[5] In addition, organoboron compounds have been used in the synthesis of new materials such as polymers and biosensors.[6] Also, organoboranes can be synthetized with simple approaches and smooth conditions.[7] Moreover, in contrast with other sources of carbon such as organostannanes[8] and organosilicon compounds,[9] organoboronic acids and esters are stable and safe and have shown to be a useful source to form carbon-carbon bonds.[10] Furthermore, the recent incorporation of trifluoroborate salts, provided further advances in terms of manipulation and robustness of the reactions.[11]

In addition, organoboron compounds have been widely used in asymmetric synthesis[12] either as reagents[13] or catalysts.[1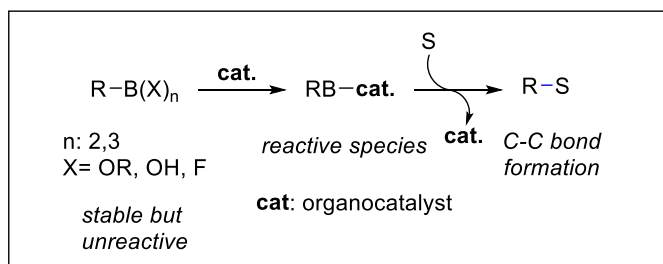4] Furthermore, asymmetric organometallic strategies based on the use of organoboronic derivatives and chiral ligands have been described.[15] The recent development of asymmetric organocatalytic methodologies with organoboranes completes the range of reactions where this type of compounds can be used. Scheme 1 shows the general sketch for organocatalytic activation of boron reagents, together with the typical transformations in which this strategy has been applied (Eq. 1 and 2). In 2005, Wu and Chong reported the first asymmetric organocatalytic C-C bond forming reaction, which introduced an alkynyl moiety in the β position of an α,β-unsaturated ketone.[16] Based on general concepts of organocatalysis,[17] they proposed that the starting achiral boronate *i* should contain two labile groups attached to the boron atom to allow transesterification with the chiral organocatalyst *ii* to give the chiral species *iii* (Scheme 2). Then, *iii* should react with the substrate (*iv*) faster than *i*, to form the C-C bond enantioselectively, affording product *v*. Ultimately, exchange of ligands would give the final product *vi* and simultaneously release the chiral organocatalyst *ii*. This paradigm allowed the development of numerous and efficient organocatalytic asymmetric strategies to form C-C bonds using organoboron compounds as synthons.

Recent reviews address this topic in great detail from the synthetic point of view[18] or either focus on a particular type of reaction[19] or catalyst.[20] Mainly, the asymmetric organocatalytic reactions developed so far have been 1,4-additions to enones **1** to afford β-substituted ketones **2** (Eq. 1, Scheme 1) and 1,2-additions to aldehydes or ketones **3** or imines **4** to generate the alcohol or amine products **5** or **6**, respectively (Eq. 2, Scheme 1). Due to the great interest of these organocatalytic organoboron-based methodologies, several groups have investigated the mechanisms with theoretical and/or experimental approaches. These studies helped to better understand the catalytic cycles and also to develop new transformations and catalysts.
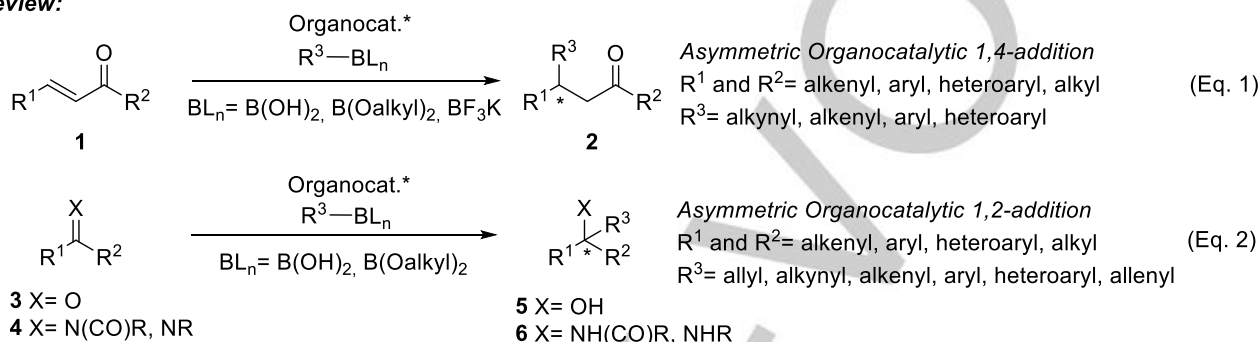
It is important to remark that, among the 1,2-additions, the Borono-Mannich reaction, also called Petasis reaction is of notable importance. The general mechanism of such reaction has been studied using different tools.[21] Although many asymmetric organocatalytic approaches have been developed for the Petasis reaction, to our knowledge no theoretical mechanistic studies have been performed yet. Therefore, the Petasis reaction is out of the scope of this review.

[a]   Dr. S. O. Simonetti, Prof. Dr. S. C. Pellegrinet
        Instituto de Química Rosario (IQUIR-CONICET), Facultad de
        Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de
        Rosario, Suipacha 531, Rosario 2000, Argentina
        E-mail: pellegrinet@iquir-conicet.gov.ar

        Supporting information for this article is given via a link at the end of
        the document.

This review:

Asymmetric Organocatalytic 1,4-addition
R^1 and R^2= alkenyl, aryl, heteroaryl, alkyl (Eq. 1)
R^3= alkynyl, alkenyl, aryl, heteroaryl

Asymmetric Organocatalytic 1,2-addition
R^1 and R^2= alkenyl, aryl, heteroaryl, alkyl (Eq. 2)
R^3= allyl, alkynyl, alkenyl, aryl, heteroaryl, allenyl

3 X= O
4 X= N(CO)R, NR

5 X= OH
6 X= NH(CO)R, NHR

Scheme 1. General organocatalytic reaction with organoboron compounds. Asymmetric organocatalytic reactions covered in this review (Eq. 1 and Eq. 2).

In this review, we have focused on the mechanistic aspects of asymmetric organocatalysis with organoboranes in C-C bond-forming reactions. In particular, we describe the theoretical and experimental mechanistic studies for asymmetric 1,4- and 1,2-additions. The former consisted in DFT calculations, while the later comprised NMR and ESI-MS studies as well as kinetic data. As a complement, in the supporting information we list further reactions that have not been theoretically investigated yet, to show the next challenges on the topic.

2. Asymmetric Organocatalytic 1,4-Additions

Asymmetric organocatalytic 1,4-additions to α,β-unsaturated carbonyl systems are the reactions for which organocatalysis with organoboronic compounds initially had the major development.[18c] The topic has evolved along with the synthesis of new chiral BINOL catalysts, mainly through the incorporation of electron withdrawing groups in C3 and C3'. While most theoretical and experimental mechanistic investigations were carried out with chiral BINOL catalysts, the mechanisms using α-hydroxy acids also have been investigated, but to a lesser extent.
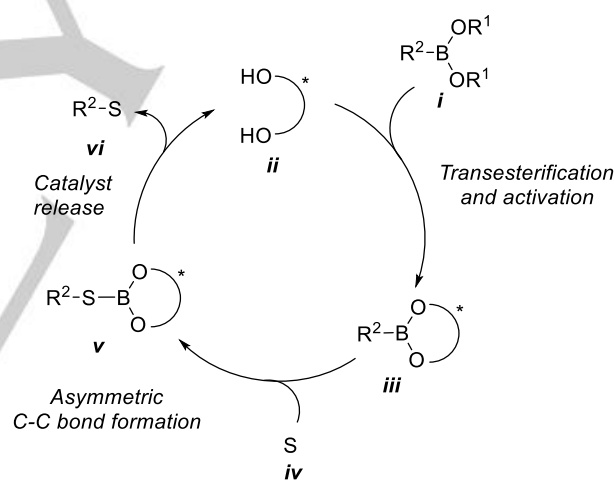
Scheme 2. General catalytic cycle of the asymmetric C-C bond formation with boronic acid and esters derivatives.

2.1. Use of chiral BINOLs

Chiral diols such as BINOLs are considered privileged structures in organocatalysis representing one of the most useful molecules to accelerate and induce asymmetry in a reaction.[22]

The seminal work that demonstrated the "proof of principle" for asymmetric organocatalytic organoboron reactions was published by Wu and Chong and consisted in the enantioselective 1,4-alkynylboration of enones with diisopropyl alkynylboronate esters **7** catalyzed by (*S*)-3,3'-diiodo-BINOL (*S*)-**9** (20 mol%) (Scheme 3).[16] The reaction was carried out with 3.0 equiv. of **7** under mild conditions. The β-substituted products **8** were obtained with yields from 78% to 97% and *ee* in the range 82 to 96%. The methodology was validated with 8 examples.

The authors proposed that the activation of the boronate species occurred by rapid transesterification with (*S*)-**9** to afford the chiral reactive species **10**, which attacks enone **1** forming the C-C bond to give product **8** with high levels of enantioselectivity.

In 2006, Pellegrinet and Goodman published the theoretical study of this reaction, representing the first theoretical study of an asymmetric organocatalytic reaction with organoboron compounds (Scheme 4). [23] The study was performed at the B3LYP/lacvp* level of theory on a model system using 3,3'-diiodo-biphenyl (*S*)-**11** instead of the corresponding BINOL (*S*)-**9**. The computed energy gap between the transition structures derived from alkynylboronate **7** (**TS18**) and the reactive species **12** (**TS17**) was *ca.* 16 kcal mol^{-1}. The difference was assigned to two structural features of alkynylboronate **12**: first, a substantial change in the C-O-B-C torsion angle that reduced the donation of electron density of the oxygen lone pairs to boron; second, the introduction of electron-withdrawing groups in the 3 and 3' positions of BINOL which pull out electron density from the oxygens, enhancing the Lewis acid character of the boron atom. As a result, alkynylboronate **12** coordinates to the enone giving complex **13**, lowering the energy barrier of the subsequent conjugate addition. Finally, the enantiomeric excess was attributed to two close contacts between one of iodines of the chiral boronate **12** and two

hydrogens of the enone in the transition structure (**TS17**) corresponding to the attack of the *Re* face. The difference of energy between the two diastereomeric transition states was in agreement with the experimental enantioselectivity. Also, the competing hetero Diels-Alder reactions towards cycloadduct **16** were computed to be disfavored by about 10 kcal mol^{-1}.
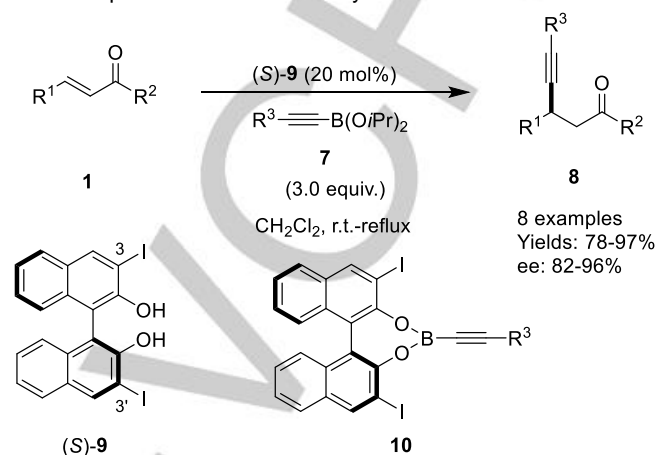
Scheme 3. Conjugate alkynylboration of enones catalyzed by (*S*)-3,3'-diiodo-BINOL (*S*)-**16**.
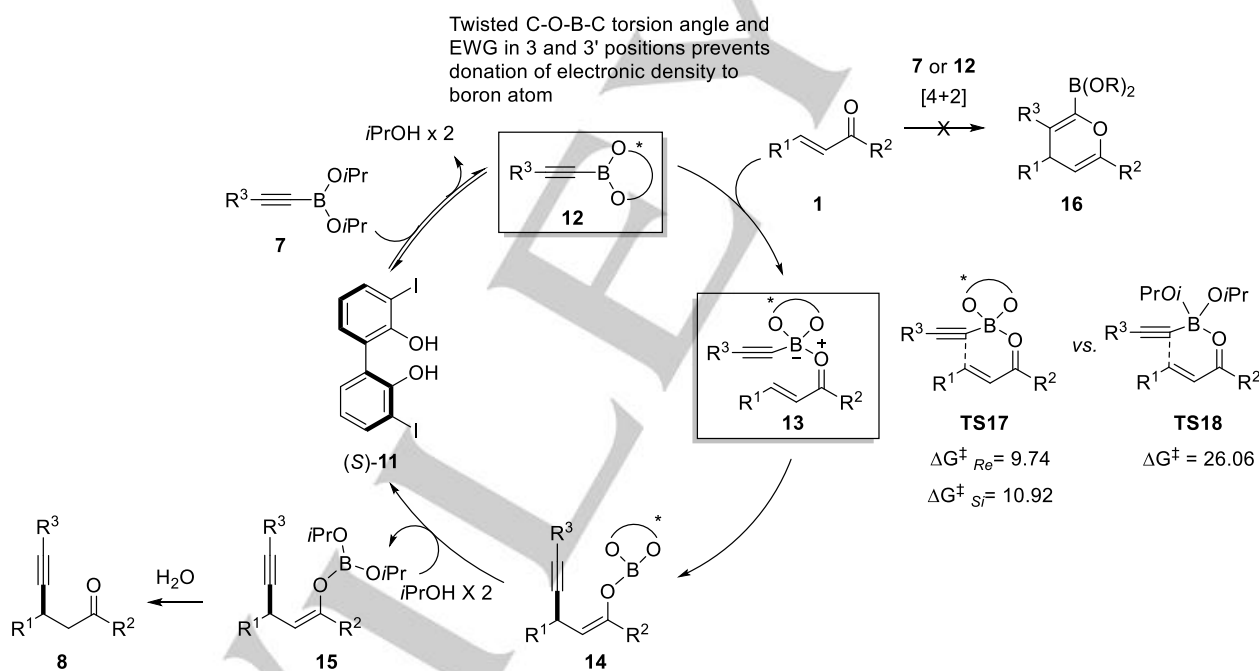
Scheme 4. Catalytic cycle for the organocatalyzed conjugate alkynylboration of enones. B3LYP/lacvp* energies in kcal mol^{-1}.

In 2007, Chong *et al.* reported the organocatalytic asymmetric conjugate alkenylation of enones **19** using dimethyl alkenylboronates **20** to afford the β-adducts **21** using (*R*)-3,3'-diiodo-BINOL (*R*)-**9** as catalyst (Scheme 5). [24] They postulated the cyclic transition state **TS22a** to account for the observed reactivity and the stereoselectivity, similar to the one found on the studies mentioned above. [23] The reaction was applied in 25 examples including aromatic and heteroaromatic ring with both

electron withdrawing and donor groups in the enone analogues and a broad substitution in the organoborane moiety.
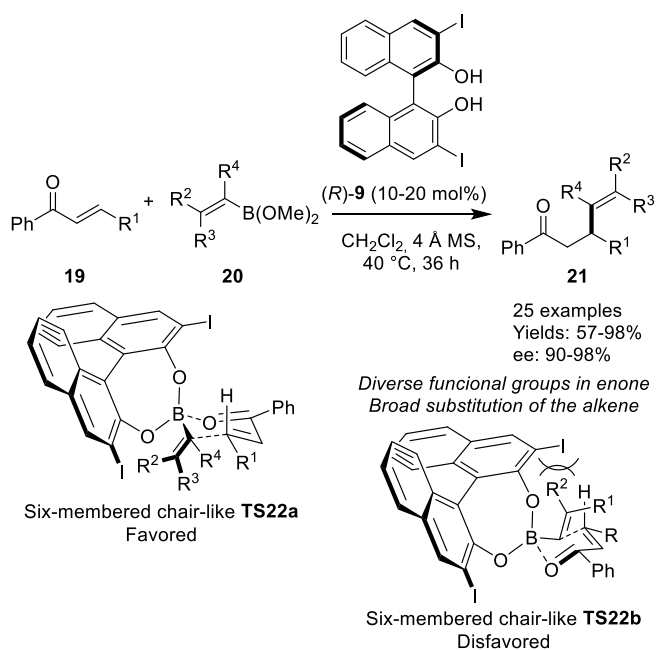
Scheme 5. Asymmetric conjugate alkenylation of enones **19** and proposed competing transition states **TS22a** and **TS22b**.

With the aim of explaining the outcome of this reaction, an exhaustive DFT study using the B3LYP/6-31G*+LANL2DZ for iodine level of theory was reported (Scheme 6).[25] The formation of the Lewis acidic alkenylboronate **24** (biphenol **11** was used as a model) has a penalty of 14.49 kcal mol^{-1} (DCM) but activates the boron species. This dioxaborolane interacts with the carbonyl moiety of the enone **25** forming the *ate*-complex **26**, lowering the energy barrier for C-C bond formation more than 17 kcal mol^{-1} relative to that for the uncatalyzed reaction (27.76 kcal mol^{-1} for **23** *vs.* 10.22 kcal mol^{-1} for **24** through **26**), *via* the sofa-like transition structure **TS27** rather than the chair-like transition structure **TS22a** originally proposed.[24] The alternative reaction channel in which only one methoxy ligand of the alkenylboronate is exchanged as well as the pathways for the competitive hetero-Diels-Alder reaction were also found to be kinetically disfavored by *ca.* 15 kcal mol^{-1} relative to conjugate alkenylboration. Single ligand exchange was first proposed by Schaus in 2006 for the asymmetric organocatalytic allylboration of ketones **3** (*vide infra*).

In 2011, May and co-workers demonstrated that the novel (*R*)-3,3'-bis-(pentafluoro-phenyl)-BINOL (*R*)-**30** organocatalyzed the addition of alkenylboronic species **20** to indole-appended enones **29** (Scheme 7).[26] The methodology provides the 1,4-addition products **31** with very good yields (60-91%) and *ee*s (87-99%). The reaction was applied to a representative spectrum of substituted alkenyl- and alkynylboronic acid derivatives and a variety of β-indole enones. Interestingly, the formation of the C-C bond is performed without protection of the indole nitrogen, an important achievement for the synthesis of natural products.[27]
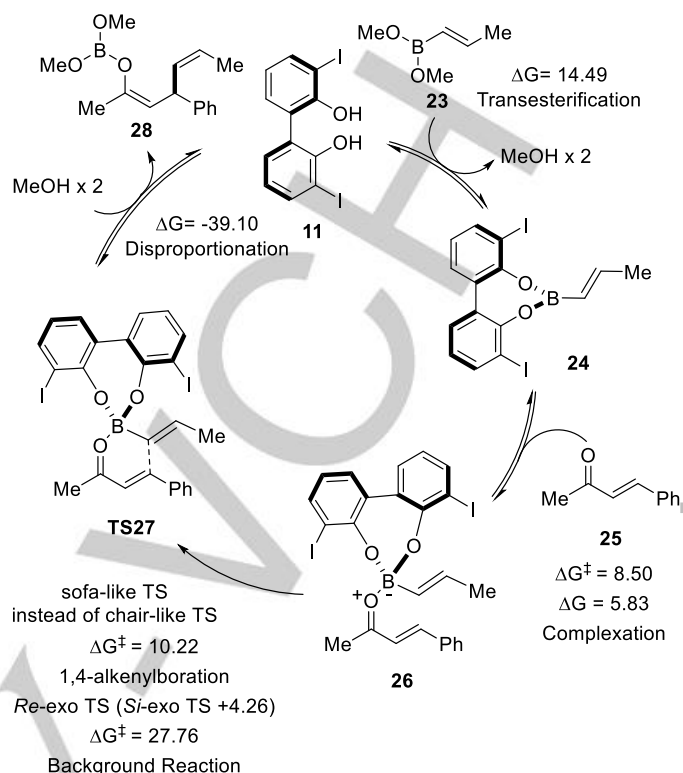
Scheme 6. DFT study of the 1,4-addition of alkenylboronates to enones mediated by chiral BINOL (*R*)-**11**. Energies in kcal mol^{-1} and DCM.

In 2012 a general and efficient method to synthetize α-chiral heterocycles using perfluorinated BINOL catalysts (*R*)-**30** (R= F) and (*R*)-**42** (R= CF$_3$) was reported (Table 1).[28] The methodology was applied to furans **32**, thiophenes **33**, pyridines **34**, quinolines **35**, pyrazines **36**, thiazoles **37**, benzothiazoles **38**, pyrroles **39**, indoles **40** and imidazoles **41**. The approach also works for electron-rich enones.
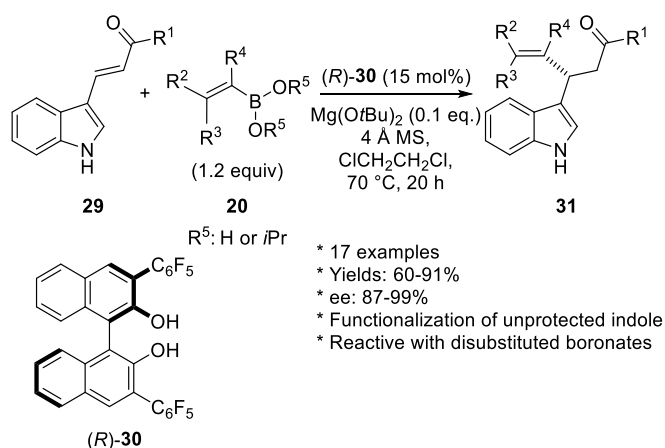

Scheme 7. Asymmetric 1,4-addition to indole-appended enones **29** catalyzed by BINOL (*R*)-**30**.

Table 1. Asymmetric 1,4-addition of alkenylboronic acids to heterocycle-appended enones.


Compounds	Yields	ee	Compounds	Yields	ee
32	(5 examples) (R)-**30**: 74-99% (R)-**42**: 75-99%	(R)-**30**: 88-98% (R)-**42**: 90-94%	**37**	(2 examples) (R)-**30**: 64-89% (R)-**42**: 82-92%	(R)-**30**: 64-89% (R)-**42**: 68%
33	(4 examples) (R)-**30**: 64-96% (R)-**42**: 90-99%	(R)-**30**: 80-88% (R)-**42**: 92-96%	**38**	(4 examples) (R)-**30**: 47-88% (R)-**42**: 69-91%	(R)-**30**: 48-60% (R)-**42**: 60-84%
34	(3 examples) (R)-**30**: 71-92% (R)-**42**: 91-95%	(R)-**30**: 72-96% (R)-**42**: 86-90%	**39**	(2 examples) (R)-**30**: 23-63% (R)-**42**: 39-90%	(R)-**30**: 84-94% (R)-**42**: 92%
35	(R)-**30**: 85% (R)-**42**: 94%	(R)-**30**: 76% (R)-**42**: 92%	**40**	(R)-**30**: 87%	(R)-**30**: 96%
36	(R)-**30**: 95% (R)-**42**: 99%	(R)-**30**: 84% (R)-**42**: 90%	**41**	(3 examples) (R)-**30**: 76-92% (R)-**42**: 83-88%	(R)-**30**: 66-92% (R)-**42**: 82%

The same group reported an experimental mechanistic study of the conjugate addition of styrylboronic acids **44** to enones **43** mediated by BINOL **42** (Scheme 8).[29] To determine the rate-determining step, they generated Hammett plots by introducing different substituents at the phenyl rings attached to the β-carbon and the carbonyl of the enone and of the styryl group of the boron nucleophile. The authors demonstrated that C-C bond formation from the complex **46** is the rate limiting step and proposed that the reaction rate depends on the stabilization of the positive charge in complex **46**. The presence of electron-rich aromatic rings conjugated to the enone accelerates the reaction by increasing the electrophilic character of the β-carbon. Also, when electron-donating groups are introduced in the phenyl ring of the styrylboronic acid, the nucleophilic attack is easier, which increase the reaction rate. Therefore, the reaction rate can be increased with the presence of electron-donating groups both in nucleophile and electrophile.
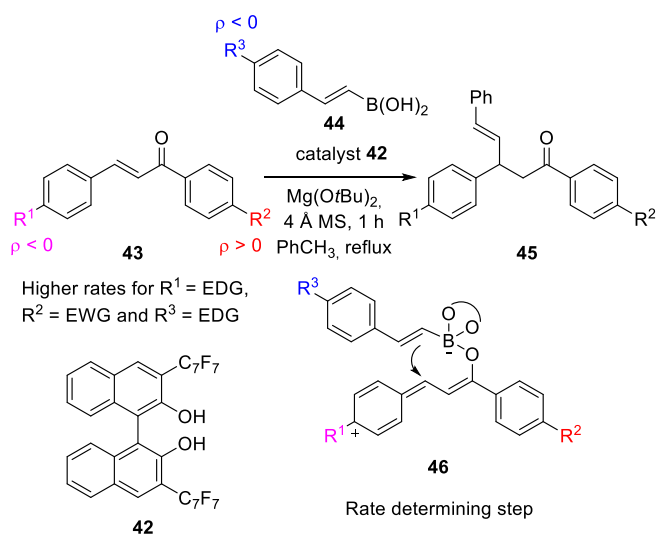
Scheme 8. Experimental mechanistic study of the addition to enones catalyzed with BINOL **42** with Hammett plots.
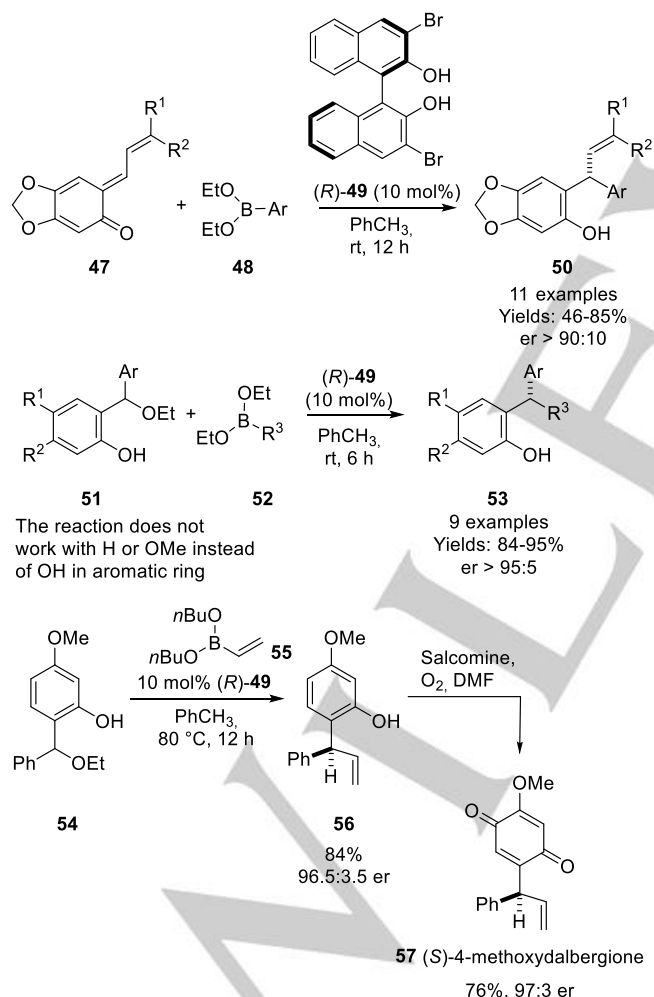
Scheme 9. Asymmetric organocatalytic functionalization of *o*-quinone methides **47** and *ortho* phenols **51** and synthesis of (*S*)-4-methoxydalbergione (*S*)-**57**.

o-Quinone methides are novel and powerful motifs used in organic synthesis.[30] (*R*)-3,3'-dibromo-BINOL (*R*)-**49** was found to catalyze the addition of arylboronates as **48** to the benzylic position of *ortho*-quinone methide **47** to yield ortho substituted phenols **50** with er higher than 90:10 (Scheme 9).[31] This versatile procedure was also extended to the reaction of hydroxybenzyl derivatives **51** with alkenylboronates **52** affording the bis-benzylic products **53** with very good yields (84-95%) and enantiomeric excesses (> 90%). Also, the authors demonstrated the key role of the hydroxyl function in the aromatic ring, since the reaction did not work when it was replaced by hydrogen or methoxyde, and thus proposed the intermediacy of a *o*-quinone methide. As an application of this methodology, (*S*)-4-methoxydalbergione (*S*)-**57**[32] was synthesized in high yield and er by treating phenol **54** with dibutyl vinylboronate **55** and catalyst (*R*)-**49**, followed by oxidation of the bis-benzylic vinyl intermediate **56** with Salcomine.

DFT calculations (optimizations at the B3LYP/6-31G** level of theory and single-points with M06-2X/LACVP**)[33] for *o*-quinone methide **61** indicated that the addition reaction proceeds *via* a sofa-like six-membered ring transition structure (**TS65**) corresponding to a Lewis acid type activation as previously observed (Scheme 10).[23,25] The mixed boronate **59** formed by exchange of one of the ligands with catalyst (*R*)-**49** was computed to be more stable that the cyclic BINOL-derived intermediate **62** and therefore was predicted to be the most abundant of the intermediate species. However, the cyclic boronate **62** gave lower energy barriers (9.5 and 14.5 kcal mol^{-1} lower for the arylboration and alkenylboration, respectively), pointing to Lewis acid activation rather than the Brønsted acid activation *via* the mixed boronate **59**. The transition structures corresponding to boronate **60** show a difference of 2.2 kcal mol^{-1} and 2.7 kcal mol^{-1} for the arylboration and the alkenylboration, respectively, favoring **TS65***Si* relative to **TS65***Re*. These differences agree with the experimentally observed enantiomeric ratios. The enantioselectivity seem to arise from destabilizing interactions between the side chain of the *o*-quinone methide and one of the bromines of the BINOL catalyst.

2.2. Use of modified tartaric acid derivatives

In 2010, Suguira and co-workers proved that *O*-monoacyl tartaric acids catalyzed the asymmetric conjugate addition of boronic acids to enones.[34] After the screening of different catalysts led to the 3,5-di(*tert*-butyl)-benzoyl derivative **68**, diverse enones **1** were subjected to the conjugate addition of alkenyl and heterocyclic boronic acids **67** (9 examples) under mild conditions (50-60 °C, 24-120 h) (Scheme 11, Eq. 1). Yields varied from 46 to 92% and *ees* from 68% to 87%.

In 2014, the strategy was extended to the asymmetric addition of styrylboronic acid **70** to dienones **69** mediated by catalyst **68** (Scheme 11, Eq. 2).[35] The monostyrylated products were obtained with moderate to high yields **71** (52-81%) and high enantiomeric excesses (86-94%) when symmetrical dienones were used. The reaction was also carried out with unsymmetrical dienones affording products **71** with *ca.* 70% yield and 87% ee. With the monostyrylated products in hand, a

ring closing metathesis with Hoveyda-Grubbs II catalyst (10 mol%) afforded the optically active cyclopentenones **72** with variable yields[36].
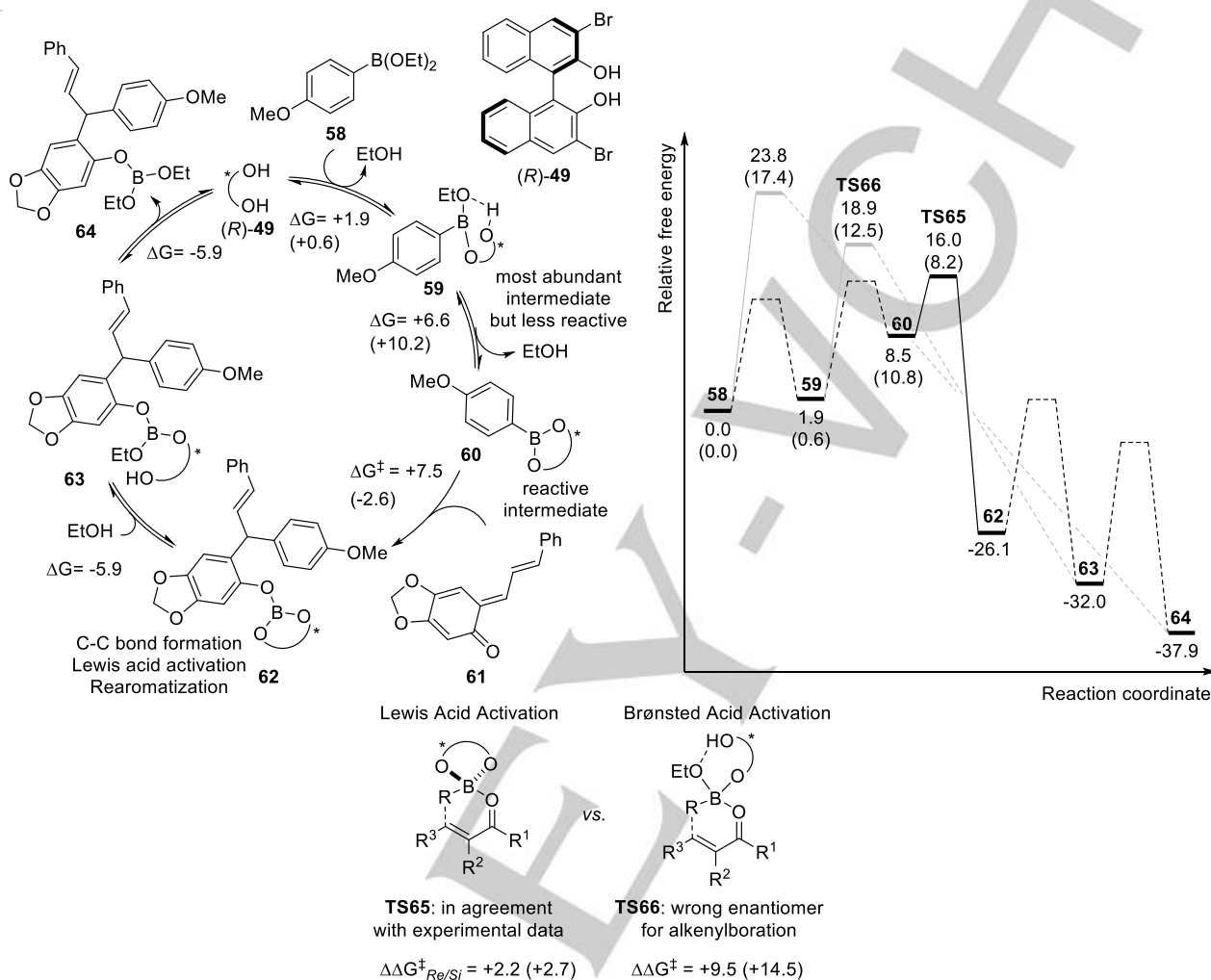

Scheme 10. DFT study of the asymmetric arylation of *o*-quinone methide with (*R*)-**49**. Free energies for alkenylboration are shown between parentheses. Energies in kcal mol⁻¹. Dotted lines are drawn for all ligand exchange steps since the corresponding transition structures were not located.

To gain insight into the mode of action of this novel catalyst, in 2014 a DFT study at the B3LYP/6-311+G** level of theory of the asymmetric conjugate alkenylboration using *O*-monoacyl L-tartaric acids **73** was reported (Scheme 12). [37] Ligand exchange of styrylboronic acid **70** with **73** affords the five membered acyloxyborane **74** (ΔG= -0.09 kcal mol⁻¹). The proposed acyloxyboranes derived from *O*-monoacyltartaric acid as reactive species were first described by Yamamoto *et al.* and used as catalysts in different reactions. [38] Then, coordination between the boron atom of **74** and the carbonyl oxygen of chalcone (**75**), gives rise to a coordination complex (ΔG‡= +18.28 kcal mol⁻¹).
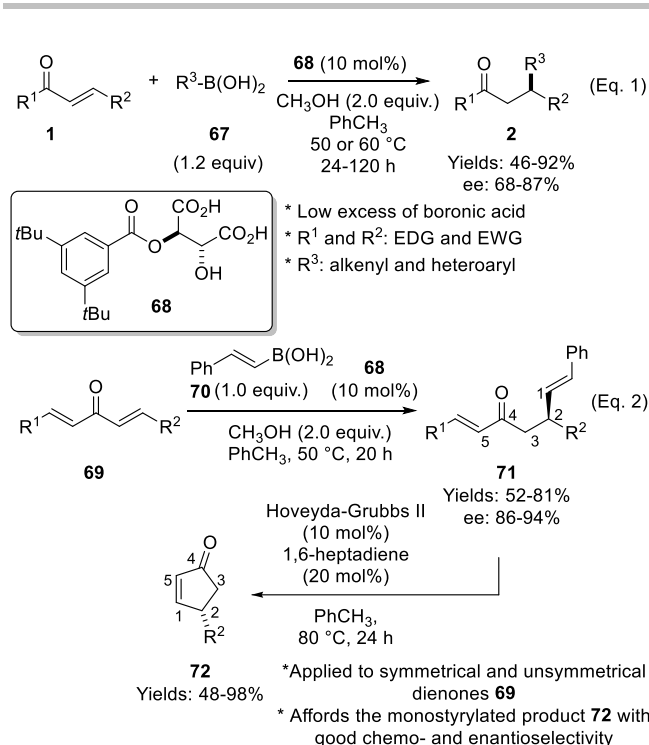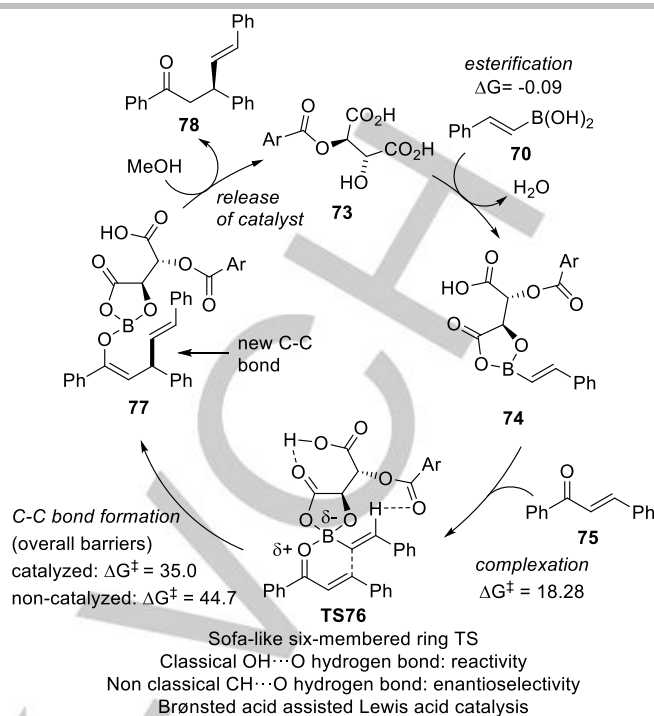
Scheme 11. Asymmetric 1,4-addition of boronic acids to enones catalyzed by tartaric acid derivative **68**. Synthesis of chiral cyclopentenones **72**.

Interestingly, the complex is stabilized by a strong hydrogen-bonding interaction (1.7 Å) between the hydrogen of the free carboxy group of the catalyst portion and the carbonyl oxygen of the cyclic acyloxyborane reducing the flexibility of the system and diminishing the energy barrier for the conjugate addition in 9.71 kcal mol^{-1} relative to the non-catalyzed reaction ($\Delta G^{\ddagger}$= 35.00 kcal mol^{-1} for **74** *via* **TS76** *vs*. $\Delta G^{\ddagger}$= 44.71 kcal mol^{-1} for **70**). A special case of intramolecular Brønsted acid assisted Lewis acid catalysis (BLA) was thus proposed.

Frontier Molecular Orbitals (FMOs) analysis of the reactants and the geometries obtained are similar to those for the BINOL-catalyzed reactions.[25] When the HOMO-LUMO gaps are calculated for the starting material **70** and for the acyloxyborane **74** reacting with chalcone **75**, no significant differences are observed (*ca.* ΔE> 4.1 eV). However, the HOMO-LUMO gap for the complex was considerably lower (ΔE= 2.47 eV). Thus, it was postulated that even if a small quantity of complex is formed, the intramolecular conjugate addition should take place promptly with formation of intermediate **77**, affording product **78** and releasing the catalyst **73**.

The study also correctly predicted the experimentally observed *S* configuration of the product **78**. The transition structure corresponding to the *Re* attack to the β carbon (**TS76**) was found to be 1.5 kcal mol^{-1} more stable than that for the *Si* approach. This energy difference was mainly attributed to nonclassical C(sp^2)-H···O hydrogen bond interactions between the carbonyl oxygen of the acyl substituent and two hydrogens of the alkenyl group.

Scheme 12. DFT study of the asymmetric 1,4-addition of phenylboronic acid to chalcones using tartaric derivative acid **73** as catalyst. Energies are in kcal mol^{-1}.

Pellegrinet and coworkers reported that α-hydroxyacids accelerate the Diels-Alder reaction of vinylboronic acid dibutyl ester **55** with cyclopentadiene (**79**) under microwave irradiation (Scheme 13).[39] When the reaction was carried out with a stoichiometric quantity of (*S*)-mandelic acid (*S*)-**80** excellent yields of **81** were obtained (93%), while 30 mol% afforded the bicyclic product with lower yield (2 h: 64%, 3 h: 72%). Unfortunately, the enantioselectivity was very low (ee <20%).
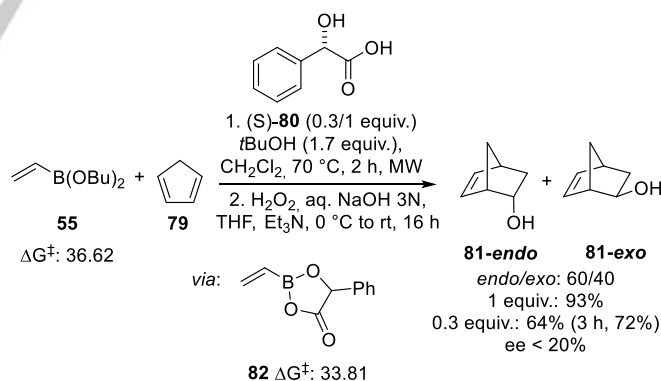
Scheme 13. Diels-Alder reaction of vinylboronic acid dibutyl ester **55** with cyclopentadiene (**79**) accelerated by (*S*)-mandelic acid (*S*)-**80**. Energies in kcal mol^{-1}.

NMR studies and DFT calculations suggested that the activation of the dienophile occured by ligand exchange to give acyloxyborane **82**. The free energy barrier for the Diels-Alder reaction of acyloxyborane **82** was computed to be *ca.* 3 kcal mol^{-1} lower than one for the background reaction (33.81 *vs.* 36.62 kcal mol^{-1} respectively) and the *endo/exo* diastereoselectivity reversed, as observed experimentally. This example demonstrated that C-C bond formation with organoboranes can

be organocatalyzed without previous coordination to the substrate.

3. Asymmetric Organocatalytic 1,2-Additions

1,2-Additions are the asymmetric organocatalytic reactions with organoboron compounds that have been developed to a greater extent, particularly in the last years. These strategies have been applied to ketones, aldehydes, *N*-acylimines, and also to isobenzopyrilium derivatives to give the enantioenriched products with high yields and enantiomeric ratios. Mostly, the catalysts comprise 3,3'-functionalized BINOLs and the derived phosphoric acids that activate the boronate moiety *via* Lewis or Brønsted acid activation. Thioureas have been used too but no mechanistic studies have been carried out so far. Several reviews about this topic cover the different strategies from a methodological point of view.[40] In this section, we describe the mechanistic studies of asymmetric organocatalytic 1,2-addition reactions, which highlight the vast diversity of strategies.

3.1. Use of chiral BINOLs

Schaus *et al.* reported the first example of asymmetric organocatalytic 1,2-addition using organoboranes in 2006[41] shortly after the report by Wu and Chong.[16] The asymmetric allylboration of ketones **3** catalyzed by (*S*)-3,3'-dibromo-BINOL (*S*)-**49** provided the tertiary homoallylic alcohols **84** enantioselectively (Scheme 14). The reaction was carried out with 15 mol% of (*S*)-**49** and a mixture of solvents (PhCF$_3$/PhMe 3:1) at low temperature.
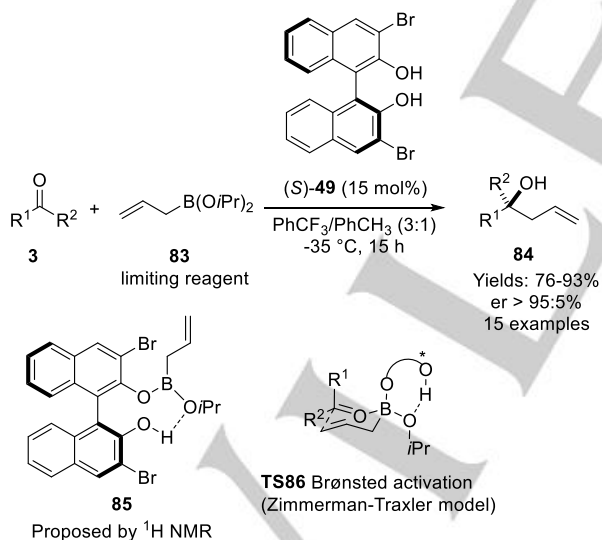

Scheme 14. Asymmetric allylboration of ketones catalyzed by (*S*)-**49**. Proposal of Brønsted-acid activation.

Different aryl and heteroaryl ketones and also α,β-unsaturated ketones were employed to obtain a broad diversity of derivatives **84** (15 examples) with very good yields (76-93%) and enantioselectivities above 95:5. In addition, the reaction of acetophenone with (*E*)- and (*Z*)-crotylboronic esters under the same conditions provided the 1,2-addition products with excellent diastereo- and enantioselectivities.

Based on ^{1}H NMR experiments, the authors observed a rapid transesterification of an isopropoxi ligand on the boron atom with a hydroxy group of the BINOL, affording intermediate **85**. This structure was proposed be responsible for the high reactivity and enantioselectivity observed in the reaction. The authors proposed that the activation of the boron species in **85** could be imparted by a hydrogen bonding between the free hydroxyl of the BINOL and the remaining isopropoxy oxygen bonded to the boron atom, leading to *Si* facial attack on the ketone in a chair-like TS model (**TS86**). Furthermore, through a kinetic study, the authors observed that the reaction was first order in catalyst, with a positive linear effect of the *ee* of catalyst in the yield and positive but nonlinear effect in *ee* of the product.

The scope of the 1,2-additions was extended to the asymmetric allylboration of acylimines **87** with diisopropyl allylboronic ester **83** catalyzed by chiral (*S*)-3,3'-diphenyl-BINOL (*S*)-**88** (Scheme 15).[42] In general, the reaction provided acylamines **90** with very good yields (76-94%) and high enantiomeric ratios (*ee*: 90 to 99%) (24 examples). However, yields and enantioselectivities for a few carbamates and aliphatic imines were considerably lower.
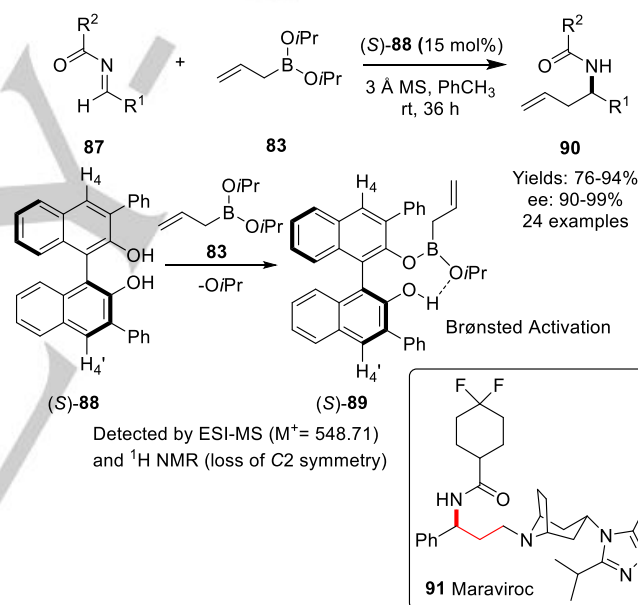
Scheme 15. Asymmetric 1,2-addition to acylimines catalyzed by (*S*)-**88**. Detection of intermediate (*S*)-**89** and structure of Maraviroc **92**.

Interestingly, the chiral BINOL that performed best for this reaction (*S*)-**88** had phenyl substituents instead of EWGs as for the examples aforementioned. The transformation was applied to an alternative route for the synthesis of Maraviroc **92**, a CCR5 antagonist against HIV.[43]

In order to understand the mechanism of the reaction, the authors carried out NMR and ESI-MS studies (Scheme 15) similar to the one mentioned above.[41] Accordingly, (*S*)-**88** was mixed with allyldiisopropoxy borane **83** and loss of C2 symmetry was observed in the NMR signals of H4 and H4'. Since the cyclic boronate proposed based on DFT studies has C2 symmetry,[23,25] the NMR signals are a clear evidence of the existence of an unsymmetrical engagement of the oxygens in

(*S*)-**89**. Moreover, intermediate **89** was observed as the predominant species in the MS experiment (M$^+$: 548.71).

In 2009, an exhaustive kinetic study about the mechanism of the asymmetric allylboration of ketones catalyzed by chiral BINOL (*S*)-**49** was reported. [44] The aim of the study was to reduce the loading of the catalyst (*S*)-**49** by evaluating the role of both the catalyst and the isopropanol in the catalytic cycle (Scheme 16).
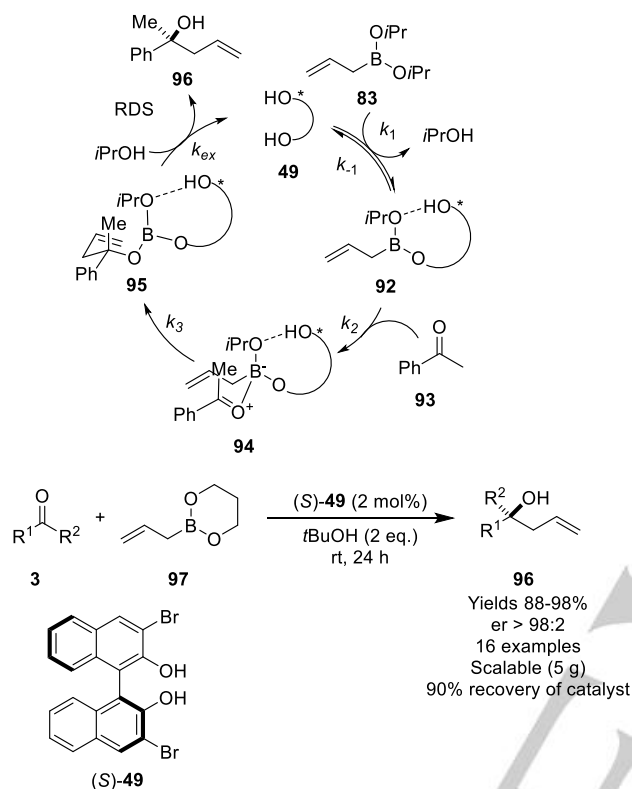

Scheme 16. Kinetic study and improvement of the asymmetric allylboration of ketones catalyzed by BINOL (*S*)-**49**.

The reaction rate and *er* were shown to increase with the concentration of isopropanol. Based on such results, the authors concluded that the rate-determining process is the final exchange of ligands that liberates the product and that the corresponding rate-constant (k_{ex}) is [*i*PrOH] dependent. As a result, the use of an external alcohol would increase the quantity of free BINOL catalyst **49** and then, less loading of catalyst would be required. Also, the use of a more stable cyclic boronate **97** would allow to increase the reaction temperature. Indeed, when the cyclic allyl boronic ester **97** and the ketone **3** were mixed in presence of 2 mol% of catalyst (*S*)-**49** and 2 equivalents of *t*BuOH at rt for 24 h, the tertiary homoallylic alcohols **96** were obtained with yields from 88 to 98% and enantiomeric ratios above 98:2 (16 examples). With this methodology, even the allylation of enolizable β-ketoesters occured efficiently. In addition, the transformation could be scaled (5 g of acetophenone) with recovery of 90% of catalyst (*S*)-**49**. The authors also demonstrated that, although the cyclic boronate **97** seems to be more sensitive to Lewis base coordination than isopropylboronate **83**, the same reaction mechanism operates.

In 2009, a computational DFT study of the organocatalyic allylboration of ketones at the B3LYP/6-31G* level of theory was published (Scheme 17). [45] The results of the calculations suggested that the chiral reactive species is the cyclic boronate **98** instead of the boronate **92** originally proposed (Schemes 15 and 16). [41,42] In agreement with the results of ^{1}H NMR experiments, the formation of **98** was computed to require 7.59 kcal mol^{-1} more than that of **92**, and therefore the latter should be more abundant. However, strong complexation to the ketone is highly favorable for **98** (ΔG= -6.87 kcal mol^{-1}) and the energy barrier for the resulting **100** (Lewis acid activation) is 4.87 kcal mol^{-1} lower than the one for intermediate **94** (Brønsted acid activation) so **98** should be the most reactive species. Furthermore, for intermediate **92** the wrong enantiomer **95** was predicted to be favored while cyclic boronate **98** afforded the correct enantiomer **102**. It is important to point out though that, as in previous studies, [23,25] the transition structures for the exchange of ligands were not located.
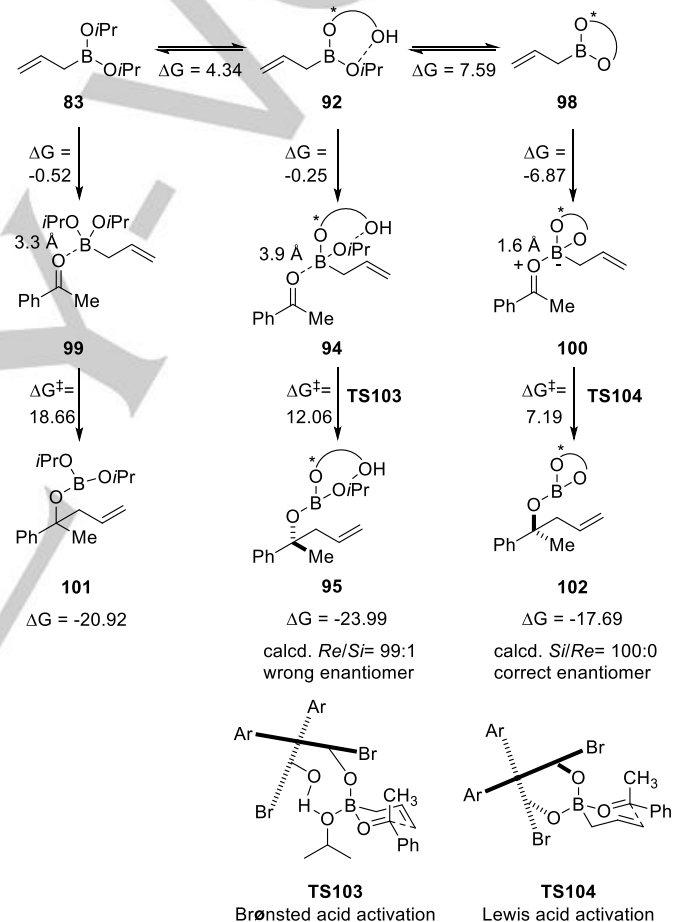
Scheme 17. DFT study of the allylboration of acetophenone: Brønsted *vs.* Lewis acid activation. Energies in kcal mol^{-1}.

With the aim of expanding the use of acylimines **106** to obtain a variety of chiral amines **107**, Schaus *et al.* were able to install diverse carbon moieties by optimizing the BINOL catalyst for each case (Scheme 18). [46] (*S*)-3,3'-Dibromo-BINOL (*S*)-**49** served as the optimal organocatalyst for the addition of arylboronates **105** (R^1= Ar) to acyl imines **106** affording 12 examples of enantioenriched acylamines **107** with yields from 70 to 98% and ee above 91%.

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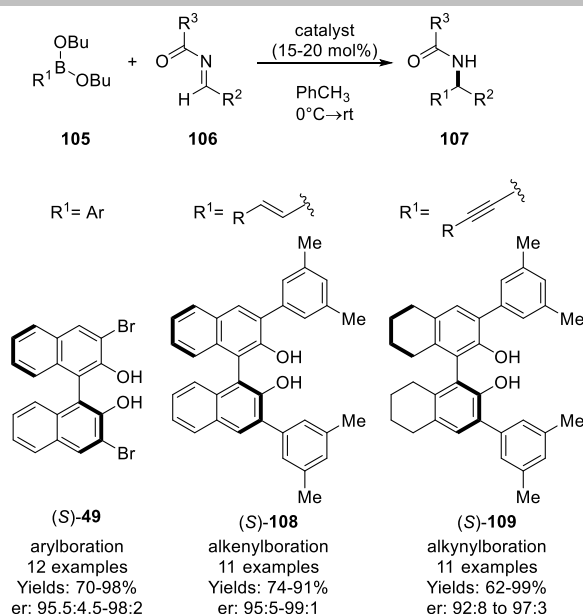
Scheme 18. Screening of chiral catalysts for additions to acylimines.

Also, (*S*)-3,3'-bis(3,5-bis(methyl)phenyl)-BINOL (*S*)-**108** catalyzed the alkenylboration of acylimines **106** obtaining the corresponding alkenyl acylamines (11 examples) with yields between 74 and 91% and ee above 90%. Moreover, for the asymmetric organocatalytic alkynylboration the octahydro analogue (*S*)-**109** was used giving the corresponding alkynyl acylamines with yields between 62 and 99% and ee higher than 86% (11 examples).
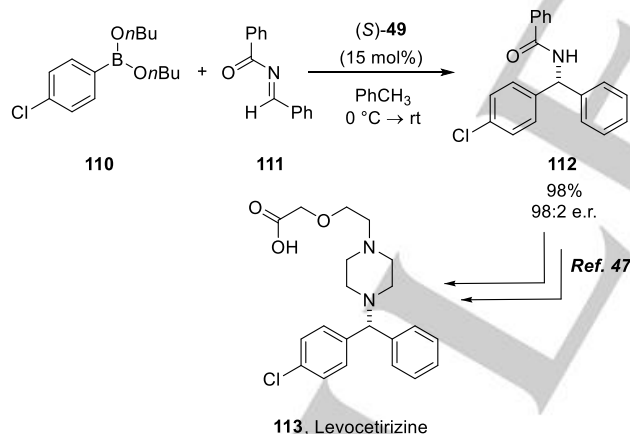
Scheme 19. Formal synthesis of levocetirizine **113**.

The methodology was used to obtain **112**, an intermediate for the formal synthesis of levocetirizine **113** (Xyzal),[47] an antihistaminic drug (Scheme 19). Reaction of *p*-chlorophenylboronate **110** and acylimine **111** afforded the diaryl intermediate **112** with 98% yield and 96% ee.

Once again, the authors attribute the catalytic activity of BINOLs to Brønsted acid activation resulting from the exchange of only one of the alcoxy goups[41] in **114** based on ESI-MS experiments, forming the intermediate **117** (Scheme 20).


117
observed by ESI-MS
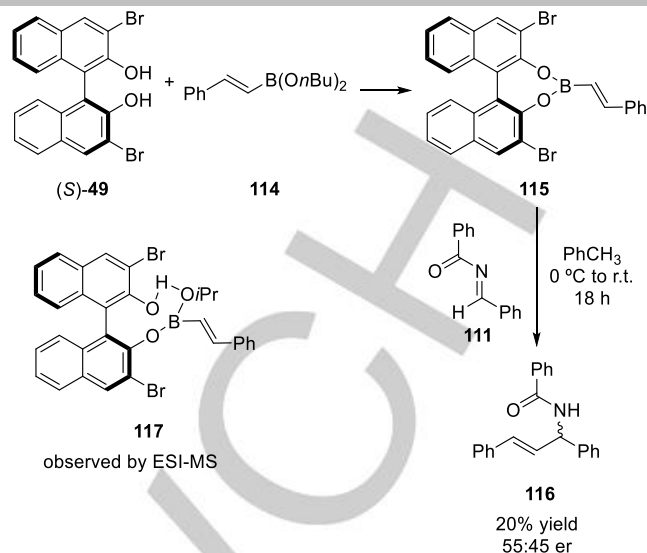
Scheme 20. Brønsted acid activation proposed for the organocatalytic reaction of acylimines.

Further evidence to support such hypothesis was obtained by synthesizing the chiral cyclic boronate **115** derived from BINOL (*S*)-**49** and (*E*)-styrylboronate **114**, which gave a yield lower than 20% and 55:45 er of **116** when reacted with benzoylbenzimine **111** under the same reaction conditions.

However, allylboration of acetophenone **93** with the allylboronate derived from 3,3'-diCF$_3$BINOL (*R*)-**117** [48] gave essentially the same er as the one obtained in the organocatalytic reaction using the 3,3'-diBr-BINOL (*S*)-**49** under similar conditions, albeit in lower yield (Scheme 21, Eqs. 1 and 2, respectively) (Scheme 21).[41]

The scope of the enantioselective organocatalyzed boronate 1,2-additions was expanded by the development of the asymmetric propargylation of ketones with allenylboronate **118** catalyzed by (*S*)-3,3'-dibromo-BINOL (*S*)-**49** (Scheme 22).[49] The reactions were run at 60 °C for 1 h under microwave irradiation in neat conditions and applied to 22 ketones with a great diversity of functional groups. When α,β-unsaturated ketones were used, complete chemoselectivity towards the 1,2-addition products **119** was observed. Yields varied between 60-98%, and the enantioselectivities were 79:21 to 99:1.
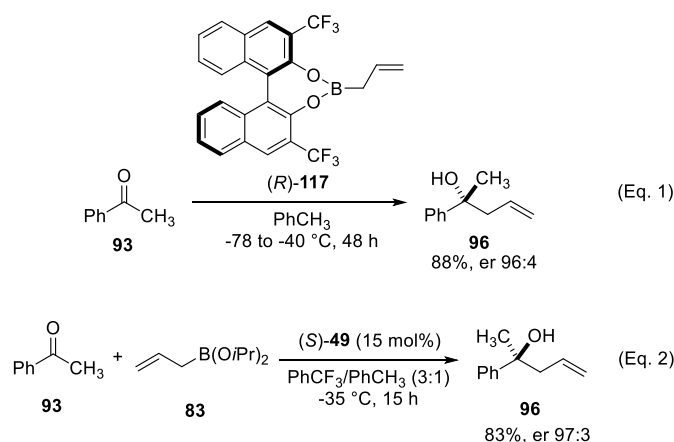

Scheme 21. Comparison of stoichiometric and catalytic asymmetric allylboration of acetophenone.

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The authors proposed a transition state based on Brønsted-activation of the organoborane. The use of racemic allenylboronic esters monosubstituted at the terminal carbon gave the *syn* products with high diastereo- and enantioselectivities, resulting from a kinetic resolution process. The observed diastereoselectivity was rationalized on the basis of the unfavorable gauche interactions of the terminal substituent with the methyl and phenyl groups of acetophenone.
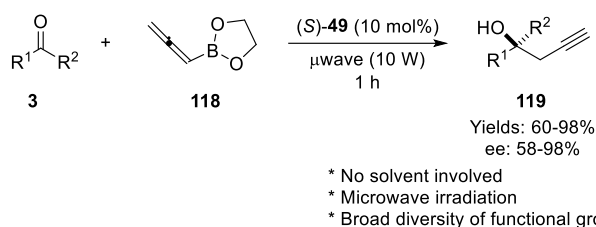
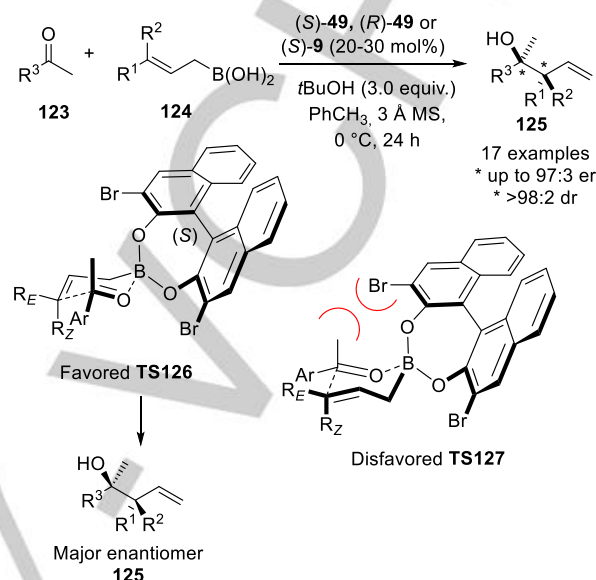**Scheme 22.** Asymmetric organocatalyzed propargylation of ketones under microwave irradiation.

This reaction was theoretically studied at the M06-2X/LACVP**//B3LYP/6-31G** level of theory and the activation was predicted to occur *via* Lewis acid catalysis rather than Brønsted acid catalysis (Scheme 23).[50] Although the TS corresponding to Brønsted activation (**TS121**) presented a free energy barrier lower than that of the background reaction **TS120** ($\Delta G^{\ddagger}$= 16.5 and 24.1 kcal mol^{-1}, respectively), this activation mode afforded the wrong enantiomer. In addition, the barrier for Lewis activation through the formation of the cyclic boronate (**TS122**) was much lower ($\Delta G^{\ddagger}$= 9.9 kcal mol^{-1}) and the predicted enantioselectivity was in accordance with the experimental results. It is important to mention though that, when the prerequisite exchange of ligands was taken into consideration, the pathway corresponding to **TS122** was computed to be preferred only by 2.9 kcal mol^{-1} using a solvation model (PCM in acetophenone).
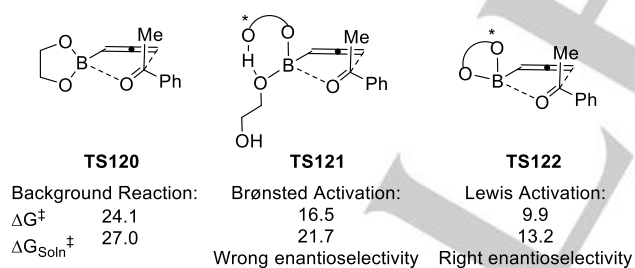
Scheme 23. Competing TSs (**TS120**-**122**) located by a DFT study of the asymmetric 1,2-adittion of allenylboronate to acetophenone. Energies in kcal mol^{-1}.

Szabó *et al.* reported the synthesis of adjacent quaternary stereocenters in **125** by asymmetric organocatalyzed allylboration of ketones **123** with γ,γ-disubstituted allylboronic acids **124** (Scheme 24).[51] Full control of the diastereo- and enantioselectivity was achieved in a stereodivergent approach by the choice of the BINOL catalyst and the diastereoisomeric prenylboronic acid. ^{19}F NMR experiments suggested the generation of the cyclic boronate derived from 3,3'-difluoroBINOL by double ligand exchange, which was accelerated by the addition of molecular sieves either in combination with *t*-BuOH or not. On the contrary, *i*-PrOH inhibited the formation of the cyclic diester, probably by esterification of the boronic acid, which was observed by ^{1}H
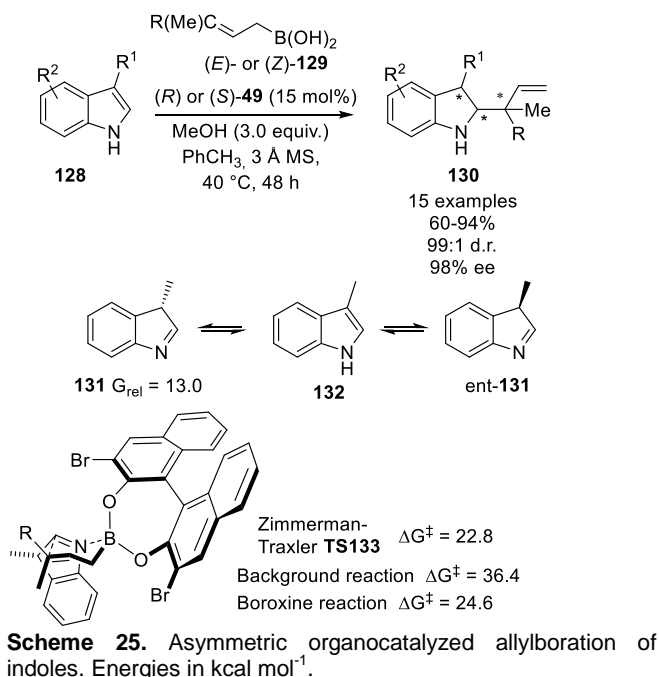
NMR. *t*-BuOH also increased the enantioselectivity probably by regenerating the BINOL catalyst. The six-membered chair-like transition structures **TS126** and **TS127** were proposed to explain the stereochemical outcome of the reactions. **TS127** leading to the minor enantiomer should be disfavored by steric repulsions between one of the susbtituents of the BINOL (X= Br in **49** or I in **9**) and the methyl group of the ketone.

**Scheme 24.** Asymmetric organocatalyzed allylboration of ketones **123**.

The reaction was later extended to the asymmetric organocatalytic allylboration of indoles **128** (Scheme 25).[52] The prenylated products **130** were obtained with high yields and stereoselectivities. Interestingly, when 3-methylindoles such as skatole (**132**) were used, three adjacent stereocenters were obtained. This work is another excellent example of functionalization of indoles without protection of the nitrogen.[31,32] The high stereoselectivity of the reaction of skatole with geranylboronic acid **129** was rationalized by a dynamic kinetic resolution of the enantiomeric imine tautomers **131** and ent-**131** and a Zimmerman-Traxler model **TS133** that minimizes the steric repulsions. The addition of an external alcohol (MeOH) was proposed to inhibit the background reaction by formation of the less reactive dimethylboronic ester and, at the same time, to facilitate the liberation of the catalyst. Dihydroisoquinoles were also prenylated efficiently under similar conditions.

A theoretical DFT study (B3LYP-D3(BJ)/6-311+G(2d,2p),SDD//B3LYP/6-31G(d,p),lanl2dz) supported the proposed mechanism and gave further insight.[53] First, the imine tautomers **131** were computed to be 13.0 kcal mol^{-1} less stable than skatole **132** (Scheme 25). In addition, exergonic dehydration of boronic acid was predicted to give the more reactive allylboroxine. However, reaction with methanol was calculated to be more favorable. The cyclic BINOL-derived boronate **TS133**, also formed by an exergonic process, exhibited higher Lewis acidity giving a more stable complex with the imine and a resulting lower energy barrier. The high stereoselectivity was correctly reproduced by the calculations and explained by steric repulsions between different substituents of the indole and either the BINOL or the allyl portion of the cyclic boronate in the less favorable approaches ($\Delta\Delta G^{\ddagger}$ > 5.8 kcal mol^{-1}).

Scheme 25. Asymmetric organocatalyzed allylboration of indoles. Energies in kcal mol^{-1}.

3.2. Use of modified BINOL-derived phosphoric acids

In 2010, Jain and Antilla reported the asymmetric allylboration of aldehydes **134** with allylboronic acid pinacol ester (**135**) catalyzed with BINOL-derived chiral phosphoric acids such as (*R*)-TRIP-PA (*R*)-**136** (Scheme 26).[54] Secondary homoallylic alcohols **137** were obtained under smooth conditions (toluene, -30 °C) with excellent yields (91-99%) and very good to excellent ees (73-99%). In addition, crotylboration of benzaldehyde was shown to take place with excellent yields and diastereo- and enantioselectivities. The authors proposed a TS with Brønsted acid activation of the boronate in which the acidic proton of the chiral phosphoric acid forms a hydrogen-bond with the pseudoequatorial oxygen of the boronate (**TS138**). This methodology paved the way to the use of chiral phosphoric acids as organocatalysts in organoborane reactions. Also, this type of Brønsted acid catalysis does not require that the organoboron compound undergoes transesterification with the chiral organocatalyst. As a result, more stable boronic esters such as pinacol derivatives can be used.
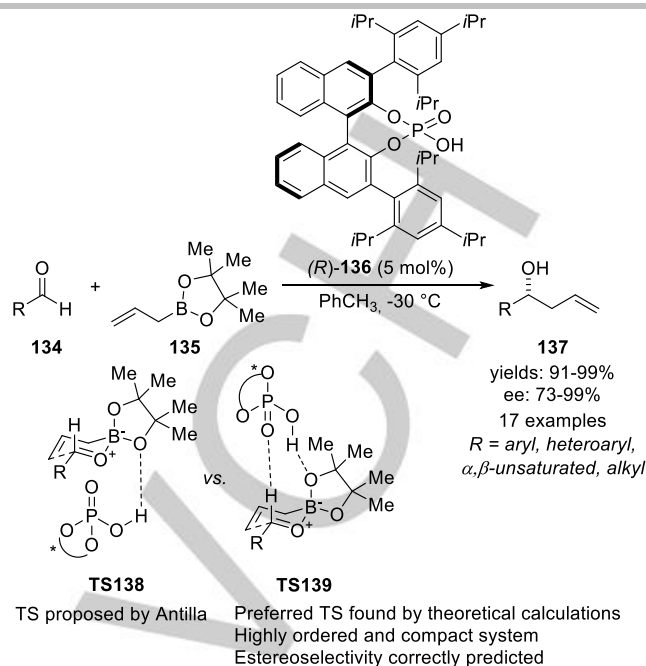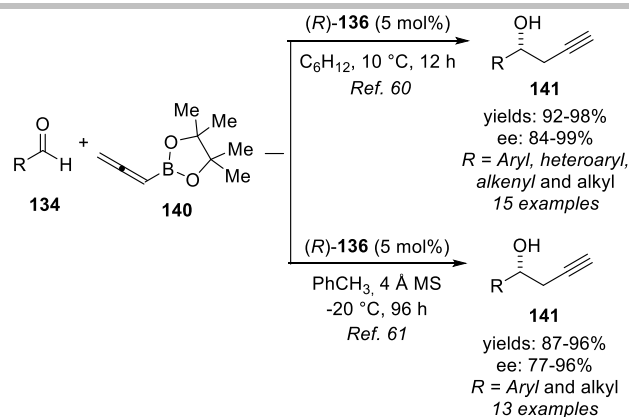

Scheme 26. Asymmetric allylboration of aldehydes catalyzed by (*R*)-**136**.

In 2012, a mechanistic study of the reaction was described.[55] Both DFT B3LYP/6-31G* calculations on a simplified biphenol model and hybrid DFT-QM/MM calculations on the whole system with ONIOM(B3LYP/6-31G**:UFF) followed by M06-2X/6-31G** single points indicated that the reaction takes place through the highly ordered and compact six-membered transition state **TS139** (Scheme 26), involving two hydrogen bonds. The chiral phosphoric acid simultaneously acts as a donor with the pseudoaxial oxygen of the boronate and as an acceptor through the non-classical interaction between the phosphoryl oxygen and the formyl hydrogen of the aldehyde. **TS139** was computed to be *ca.* 3 kcal mol^{-1} more stable than the TS originally proposed (**TS138**) and 6 kcal mol^{-1} lower in energy than the one for the background reaction.[54] Moreover, the model correctly reproduced the observed enantioselectivity, which also helped correct the missassigned absolute configuration of one of the products.[56]

In 2012, the groups of Antilla and Reddy almost simultaneously reported the asymmetric 1,2-addition of allenylpinacol boronate (**140**) to aldehydes **134** to form the homopropargylic alcohols **141** with excellent yields and enantioselectivities (Scheme 27).[57,58]

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Scheme 27. Asymmetric propargylation of aldehydes catalyzed by phosphoric acid (R)-**136**.

The authors proposed different transition structures to explain the experimental results (Scheme 28). Antilla and coworkers proposed single-point binding of the chiral phosphoric acid to the pseudoequatorial oxygen of the boronate (**TS143**) and located the corresponding transition structures computationally using a biphenol model. On the other hand, Reddy proposed Brønsted acid activation of the aldehyde with simultaneous H-bonding between the phosphoryl oxygen and the hydrogen atom of the formyl group (**TS 144**). A theoretical study at the M06-2X/LACVP**//B3LYP/6-31G* level of theory first investigated the preferred reaction pathway using buta-1,3-diene-1,4-diol-phosphoric acid (**145**) as a model for the catalyst.[59] The results were refined with the biphenol model previously used by Antilla *et al.* and finally with the full catalyst. The calculations indicated that the TS for the background reaction **TS142** as well as **TS143** and **TS 144** were more than 5 kcal mol⁻¹ higher in energy than the TSs in which the pseudoaxial oxygen of the boronate is activated by the acidic hydrogen of the catalyst and the hydrogen of the aldehyde interacts with phosphoryl oxygen (**TS146**, Goodman model). Also, the energy difference between **TS146*Si*** and **TS146*Re*** accurately explained the observed enantiomeric ratio. The Antilla-Houk's model predicted the wrong stereochemistry but was proposed as the preferred pathway to the minor product.

Later, Antilla, Houk and coworkers reinvestigated the mechanism of the enantioselective allylation and propargylation reactions catalyzed by (R)-TRIP-PA (R)-**136** at different DFT levels of theory (B3LYP and B3LYP-D3/6-31G*). The results were coincident with those obtained by Goodman *et al.* and provided further insight to rationalize the experimental enantioselectivity.[60]
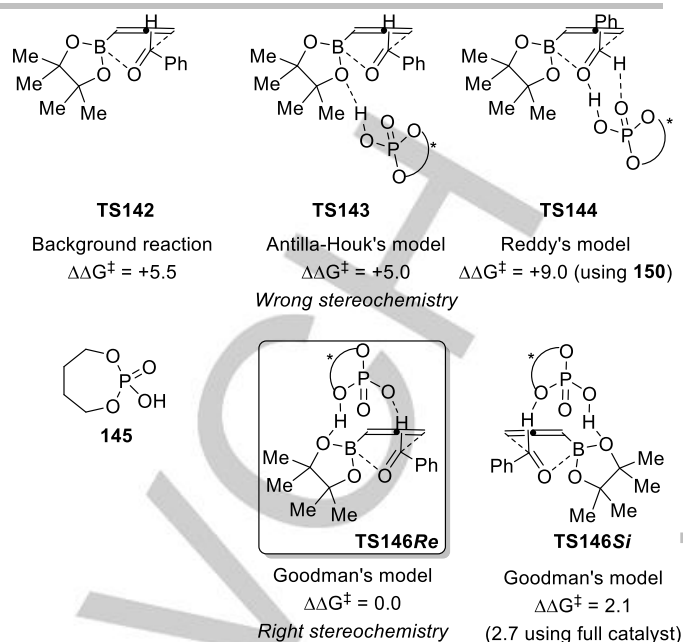
Scheme 28. Theoretical study of the propargylboration of aldehydes catalyzed by (R)-**136**. Energies in kcal mol⁻¹ using biphenol model unless otherwise noted.

Malkov *et al.* used chiral Brønsted acid catalyst (R)-TRIP-PA (R)-**136** to obtain *Z*-homoallylic alcohols **148** through kinetic resolution of racemic α-substituted pinacol allylboronates (±)-**147** (Scheme 29).[61] DFT calculations were performed to optimize the *E/Z* ratios by the *in silico* design of the boronate moiety.
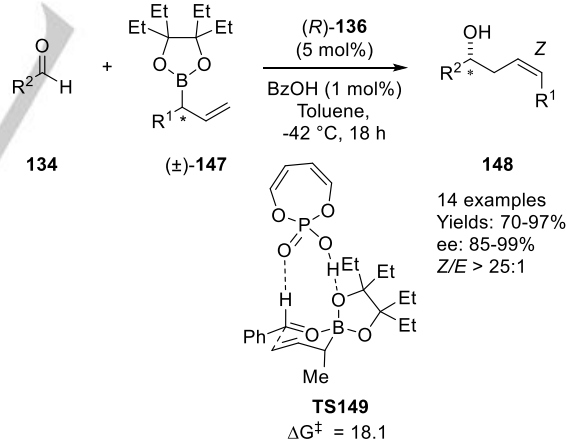
Scheme 29. Enantioselective synthesis of *Z*-homoallylic alcohols catalyzed by (R)-**136**. Energies in kcal mol⁻¹.

They predicted that the more selective synthon was the tetraethylethylene glycol boronate **147** and found that the preferred TS (**TS149**) corresponded to the Goodman's model,[55] which was *ca.* 2 kcal mol⁻¹ lower that the TS leading to the *E* isomer. This result was experimentally validated affording a 97:3 *Z/E* ratio. The methodology was applied to obtain 14 homoallylic alcohol derivatives with yields in the range 70-97% and ee of 85-99% with a remarkable preference for the *Z* isomer (*E/Z* >25:1).

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Summary

Asymmetric organocatalytic C-C bond forming reactions with organoboron compounds constitute a prominent area of organic chemistry and this topic has been growing exponentially in the last years both in number of publications and in impact. While the development of methodologies with boronic acid derivatives has been extensively advanced, attempts to elucidate the reaction mechanisms are more limited. This review highlights the progress that has been made in this area. Mechanistic studies were carried out theoretically with the aid of DFT calculations and experimentally using different techniques (NMR and ESI-MS, kinetic measurements, etc.). All of these were very useful to identify the most abundant and/or the most reactive species as well as the rate-determining step within the catalytic cycle which, in turn, helped improve the efficiency and the selectivity of the reactions. A deep insight into the numerous factors that affect the reaction mechanisms, such as the coordination with the catalyst, the role of the additives and the properties of the transition structures, is crucial for further development. So, what are the lessons learned so far? Here, we summarize some generalities drawn from mechanistic studies covered in this review:

1. It appears that for BINOL-catalyzed reactions, the most abundant species is the product of a single ligand exchange process between the organoboron compound and the catalyst, which is activated by an internal H-bond (Brønsted acid activation), while the more reactive intermediate is the cyclic boronate formed by double ligand exchange process (Lewis acid activation). Such compound is highly electrophilic due to its distorted geometry which prevents that the oxygens donate electron density into the vacant p orbital on boron, facilitating the tight coordination to the substrate and the subsequent step of addition.

2. When α-hydroxyacids are used as catalysts, the reactive species seems to be the five-membered acyloxyborane, activated by the carbonyl and in some cases by an additional intramolecular H-bond. Complexation to the substrate enhances the rate of the addition. However, α-hydroxyacids also accelerate reactions in which such step is not possible due to the lack of a heteroatom in the substrate.

3. BINOL-derived phosphoric acids are Brønsted acid catalysts that protonate the pseudoaxial oxygen of the boronate and also experience weaker H-bond interactions (for instance between the phosphoryl oxygen and the formyl hydrogen of aldehydes) that make the system more rigid.

4. While BINOL and α-hydroxyacid catalysts require boronic esters that can exchange ligands, BINOL-derived phosphoric acids are used with stable boron counterparts.

5. The additive alcohol might serve to suppress the competitive background reaction by generating a less reactive boronic ester derivative and/or to release the organocatalyst from the product of addition.

6. The C-C bond forming addition seems to be the rate-determining step although the exchange of ligands might compete.

7. In general, the key addition step exhibits a closed six-membered ring transition structure, in which the boron atom and at least one heteroatom are part of the ring. The geometries vary from sofa-like to chair-like structures, depending on the structure of the substrate and the carbon substituent in the organoboron compound.

8. The enantioselectivity is dictated by a fine combination of effects but generally dominated by steric clashes generated by the substituents of the chiral catalyst.

9. Whilst the first theoretical calculations were initially performed with low cost theory levels using simplified models, thanks to the continuing progress of theory and computation today more accurate results can often be obtained using the complete chemical systems with higher levels of theory. In any case, it should be always kept in mind that theoretical calculation only provide a complementary (though very useful) practice to analyze, rationalize and predict the outcome of experiments.

The mechanism of many asymmetric organocatalytic C-C bond forming reactions have not been theoretically studied yet, such as the asymmetric Petasis reactions or the use of thioureas catalysts or trifluoroborate salts. Those that have not been cited in this minireview are listed in the Supporting Information. Hopefully, this review will contribute to bring further attention and generate new concepts in this fertile area of organic chemistry.

Sebastián O. Simonetti was born in Chabas (Santa Fe, Argentina) and received his B. Sc. degree in Chemistry in 2011 from the National University of Rosario (UNR), and his PhD in 2016, as a Doctoral Fellow of the National Research Council (CONICET) at the Institute of Chemistry Rosario (IQUIR, CONICET-UNR) under the supervision of Dr. Kaufman. In 2016, he joined Dr. Pellegrinet's group and focused on the asymmetric organocatalytic reactions with organoboranes. In 2017, he was awarded a Fellowship of the Alexander von Humboldt Foundation at the Max Planck Institute of Colloids and Interfaces in Germany under the supervision of Dr. Pfrengle to synthetize fragments of oligosaccharides belonging to the plant cell wall, returning to IQUIR in 2018. His research interests include the total synthesis of bioactive heterocyclic natural products and the study of reactions of glycosides with interesting biological activity.
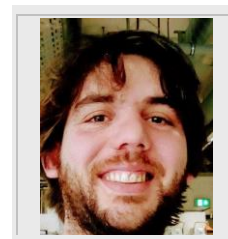
Silvina C. Pellegrinet studied Chemistry at the National University of Rosario (B. Sc. 1995 and PhD 1999). During her PhD she worked on total synthesis under the supervision of Dr. Spanevello. She then conducted postdoctoral research on the study of different cyclization reactions under the supervision of Dr. Goodman in the Department of Chemistry of the University of Cambridge (UK). In 2001, she returned to Argentina as a Postdoctoral Fellow with Dr. Rúveda. Since 2002, she has been working on the study, design and development of organoborane

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reactions. Silvina has been an Assistant Professor since 2011. Her research interests include different aspects of organic chemistry such as asymmetric synthesis, organocatalysis, pericyclic reactions, organoboron compounds and computational chemistry.

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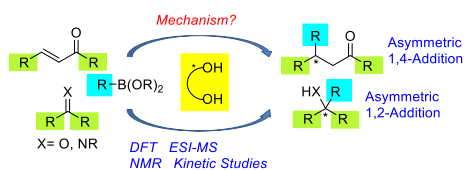
Asymmetric organocatalytic additions can be carried out with different organoboron compounds to give products with very good yields and enantiomeric ratios. Herein, we describe the mechanisms that have been proposed based on theoretical and experimental studies for asymmetric organocatalytic C-C bond forming reactions with organoboron compounds.

Organocatalysis - Organoboranes

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Asymmetric Organocatalytic C-C Bond Forming Reactions with Organoboranes: A Mechanistic Survey

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