Cycloaddition Hot Paper

How to cite:
International Edition: doi.org/10.1002/anie.202000652
German Edition: doi.org/10.1002/ange.202000652

# Stereoselective [4+2]-Cycloaddition with Chiral Alkenylboranes

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***Abstract:*** *A method for the stereoselective [4+2]-cycloaddition of alkenylboranes and dienes is presented. This transformation was accomplished through the introduction of a new strategy that involves the use of chiral N-protonated alkenyl oxazaborolidines as dieneophiles. The reaction leads to the formation of products that can be readily derivatized to more complex structural motifs through stereospecific transformations of the C–B bond such as oxidation and homologation. Detailed computation evaluation of the reaction has uncovered a surprising role of the counterion on stereoselectivity.*

## Introduction

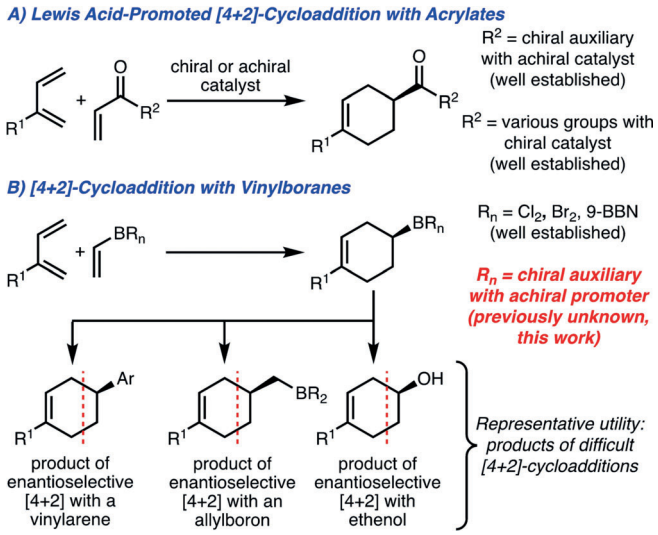
The [4+2]-cycloaddition is an important method in modern organic chemical synthesis due to the facility with which a diverse range of cyclohexene rings can be constructed.[1] A key milestone in the development of [4+2]-cycloadditions was the identification of chiral auxiliaries with acrylate-based dieneophiles that allow control of absolute stereochemistry.[2] These advances ultimately paved the way for the introduction of chiral catalysts to control the enantioselectivity of the cycloaddition (Scheme 1 A).[3]

Additional progress in the field of [4+2]-cycloadditions led to the realization that other electron-deficient alkenes would undergo reaction at reasonable rates.[4] This ultimately led to the development of alkenylborane cycloadditions, which was first described by Matteson and Waldbilling in 1963 (Scheme 1 B).[5–9] In sharp contrast to reaction of unsaturated carbonyls, the translation of alkenylborane [4+2]-cycloadditions to the realm of enantioselective synthesis has yet to be achieved with high selectivity. Development of such a process would render unknown enantioselective [4+2] cycloadditions attainable through stereospecific transformation of the C–B bond.[10] For example, enantioselective [4+2]-cycloadditions of alkenylarenes and dienes are unknown, but could be formally accomplished through [4+2]-cycloaddition with alkenylboranes and subsequent stereospecific cross-coupling with aryl halides (Scheme 1 B).

Several reports have described the development of stereoselective [4+2]-cycloadditions with chiral vinylboranes (Scheme 2 B).[5h,r,z,ab,6e] In 1997, Avery and co-workers reported the reaction of vinylborane **1** with isoprene to provide the cycloadduct in 63:33 er after oxidation. Due to the use of a boronate ester, high reaction temperature was necessary, which may be detrimental to selectivity.[5r] More recently, Pisanao and Pellegrinet described the cycloaddition of (+)-2-carene derived vinylborane **2** with cyclopentadiene to generate the product in 70:30 er after oxidation.[5z] Since the more reactive alkylhalovinylborane was used, the reaction temperatures were significantly lower compared to use of a boronate ester. However, the lack of rigidity due to the rotatable alkyl–B bond may be, in part, the source of the moderate facial selectivity.[6e]

## Results and Discussion

To develop an auxiliary that combines the characteristics of high reactivity (low-lying LUMO) and rigidity, the strategy shown in Scheme 2 B was explored. It was reasoned that if an alkenyl oxazaborolidine could be protonated with a Brønsted acid, cationic adduct **5** would be generated that would possess




***Scheme 1.*** Key developments in [4+2]-cycloadditions.

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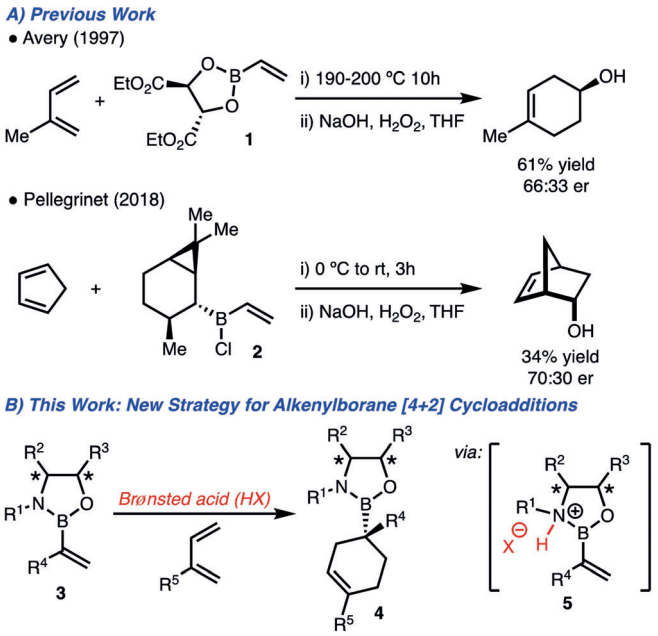
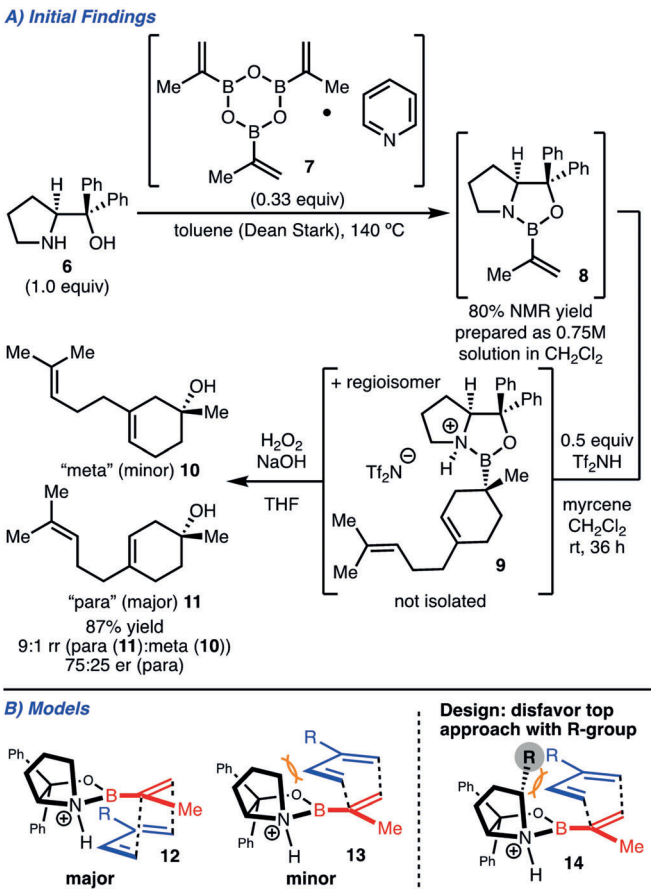



***Scheme 2.*** Strategies for stereoselective [4+2]-cycloaddition with chiral alkenylboranes.




***Scheme 3.*** Initial Studies.

the features of high reactivity and rigidity. Initial efforts were directed towards the use of diphenylprolinol (**6**)-derived alkenylboranes for several reasons: 1) related aryl and alkyl oxazaborolidines are known to be stable since they have been used as pre-catalysts for a variety of enantioselective transformations.[3b,11] 2) Activation of aryl oxazaborolidine with Lewis acids or Brønsted acids has been demonstrated.[11] 3) Diphenylprolinol is commercially available and costs less than $\$2\,g^{-1}$ from a variety of suppliers; furthermore derivatives are easily prepared from proline.

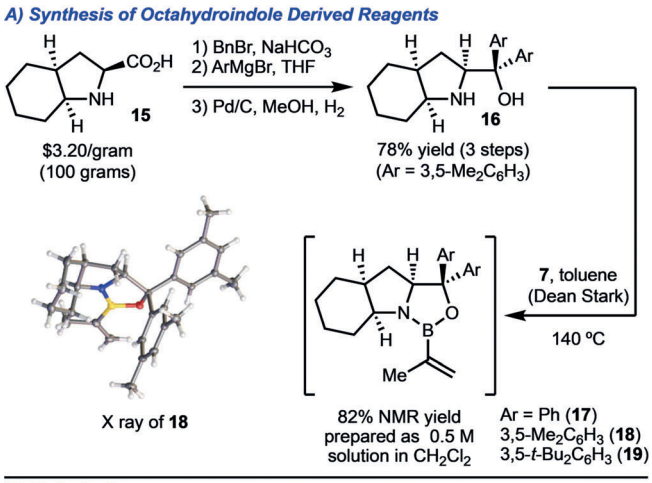
Synthesis of alkenyl oxazaborolidine **8** was readily achieved in high yield through azeotropic removal of water from an equimolar mixture of alkenylboroxine pyridine complex **7**[12] and diphenylprolinol (**6**). The generated alkenyl oxazaborolidine **8** was used without purification as a solution in dichloromethane. Early studies revealed that addition of $Tf_2NH$ to oxazaborolidine **8** and myrcene led to formation of the cycloadducts **10** and **11** after oxidation. While the enantioselectivity for the major regioisomer **11** is moderate (75:25), it was encouraging and served as a proof of concept and starting point for further optimization. Based on the absolute stereochemistry of product **11**, it was proposed that the major stereoisomer is generated when the diene approaches the bottom face of the alkenylborane as shown in **12** (Scheme 3B). Conversely, the minor stereoisomer is likely formed by approach of the diene from the top face (**13**). To design a more effective chiral auxiliary, we hypothesized that placement of a substituent on the concave face of the 5/5-ring system could further disfavor approach from the top face, thus enhancing facial selectivity (see **14**).

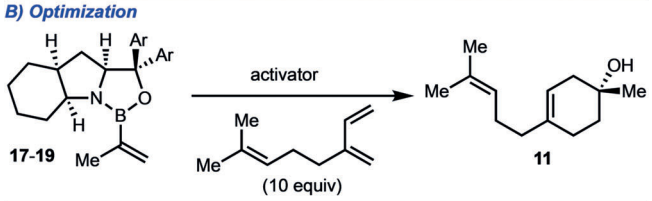
Based on the hypothesis outlined in Scheme 3B (**14**), an auxiliary based on commercially available L-octahydroindole-2-carboxylic acid (**15**) was selected. The amino alcohol **16** was easily prepared in three steps on a multigram scale without the aid of chromatographic purification (Scheme 4A). The simplicity of this synthesis enables facile derivatization of the chiral auxiliary. Condensation with the alkenylboroxine pyridine complex **7** led to formation of the oxazaborolidine **18** in good yield.

With access to alkenylborane **17**, cycloaddition with myrcene led to the formation of product **11** with good yield, and importantly, improved selectivity (Scheme 4B, entry 1) when compared to reactions with **8**. While reactions performed at lower temperatures resulted in higher selectivity, the yield was diminished due to incomplete conversion (Scheme 4B, entries 2–3). Reaction optimization through modulation of the Brønsted or Lewis acid activator was ineffective (Scheme 4B, entries 4–7). Steric modulation of the aryl units resulted in an increase in enantioselectivity, but with a concomitant decrease in yield (Scheme 4B, entry 8). Fortunately, the yield was improved through the use of 1.0 equiv of $Tf_2NH$ (Scheme 4B, entry 9).

Having optimized the conditions for this reaction, a variety of dienes were evaluated with alkenylborane **18**. As shown in Scheme 5, 2-alkyl- and 2-aryl-substituted dienes underwent reaction with high selectivity (products **11**, **21**—**23**, and **25**–**31**). Cyclopentadiene also functioned well to generate **24** with high levels of diastereo- and enantioselectivity. Vinyl oxazaborolidine **20** could also be used and enabled the highly enantioselective synthesis of products **32**–**36**. Particularly successful was the use of 2-phenyl butadiene, since product **35**

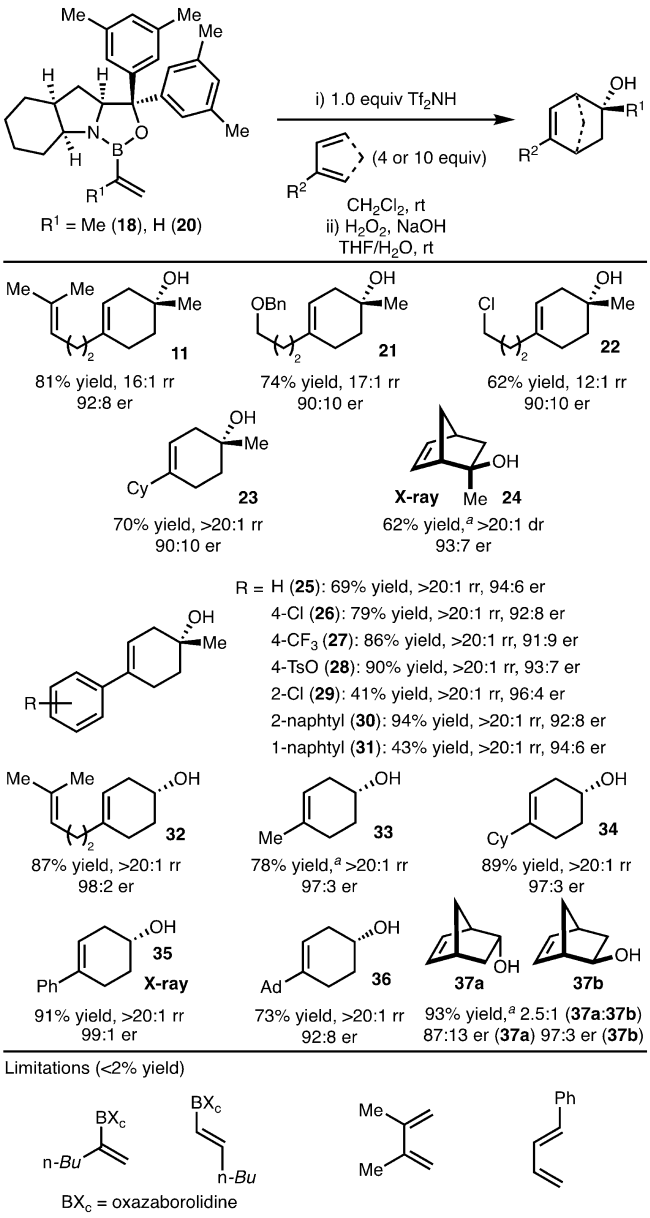
  




| entry | reagent | activator | temp (°C) | rr[a] | yield[b] | er[d] |
|---|---|---|---|---|---|---|
| 1 | **17** | 0.5 equiv $Tf_2NH$ | 22 °C | 18:1 | 82% | 89:11 |
| 2 | **17** | 0.5 equiv $Tf_2NH$ | 10 °C | 18:1 | 41% | 91:9 |
| 3 | **17** | 0.5 equiv $Tf_2NH$ | 0 °C | 19:1 | 8% | 93:7 |
| 4 | **17** | 0.5 equiv TFA | 22 °C | nd | <2%[c] | nd |
| 5 | **17** | 0.5 equiv TfOH | 22 °C | nd | <2%[c] | nd |
| 6 | **17** | 0.5 equiv $BBr_3$ | 22 °C | 1:2 | 10%[c] | nd |
| 7 | **17** | 0.5 equiv $AlBr_3$ | 22 °C | 11:1 | 10%[c] | nd |
| 8 | **18** | 0.5 equiv $Tf_2NH$ | 22 °C | 17:1 | 51% | 92:8 |
| 9 | **18** | 1.0 equiv $Tf_2NH$ | 22 °C | 16:1 | 81% | 92:8 |
| 10 | **19** | 0.5 equiv $Tf_2NH$ | 22 °C | 6:1 | 24% | nd |

***Scheme 4.*** A) Synthesis octahydroindole-derived reagents.[21] B) Optimization of the [4+2]-cycloaddition. [a] Regioisomeric ratio (rr) of *para* (**11**) to *meta* (**10**) isomers. [b] Yield of product after isolation by silica gel column chromatrogaphy. [c] Yield determined by analysis of the unpurified reaction mixture by $^1$H NMR. [d] Enantiomeric ratio (er) is of the *para* isomer (**11**) and was determined by HPLC analysis with a chiral column after derivatization.

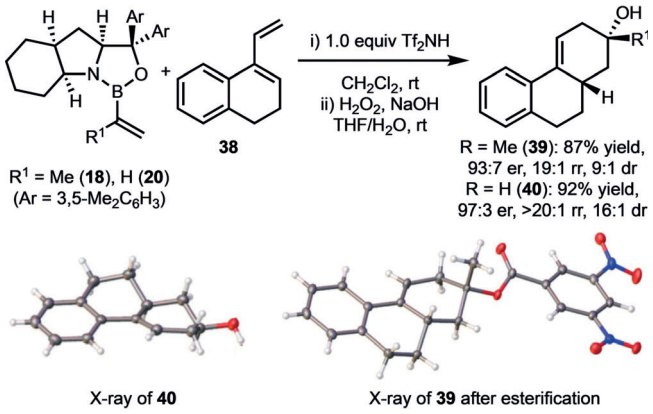



***Scheme 5.*** Substrate scope. Yield of product after isolation by silica gel column chromatrogaphy are shown and are the average of two runs. Regioisomeric ratio (rr) is of *para* to *meta* isomers. Enantiomeric ratio (er) is of the *para* isomer and was determined by HPLC analysis with a chiral column after derivatization. [a] Due to sample volatility, yield determined by analysis of the unpurified reaction mixture by $^1$H NMR with an internal standard.

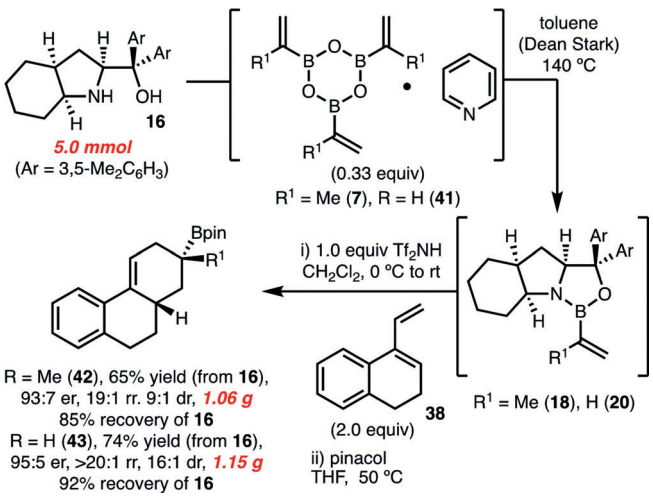
was generated in 99:1 er. In the case of cyclopentadiene, a mixture of *endo*- and *exo*-diastereomers **37a** and **37b** was formed. This stands in contrast to the reaction of isopropenyl borane **18** with cyclopentadiene, in which a single observable diastereomer was formed (product **24**). While high levels of enantioselectivity are achieved for many examples, limitations were uncovered when the alkenylborane was substituted for any group other than a methyl at the 1-position, likely for steric reasons. For example, reaction of an oxazaborolidene in which $R^1 = {}^n$Bu or substitution at the 2-position did not give product formation. In addition, 1-substiuted or 2,3-disubstituted dienes were not tolerated.

Cycloadditions of 1,2-disubstituted diene **38** with **18** or **20** enabled the synthesis of **39** or **40**, respectively, with high levels of enantio- and diastereoselectivity (Scheme 6). The absolute configuration of each was confirmed by X-ray crystallography.

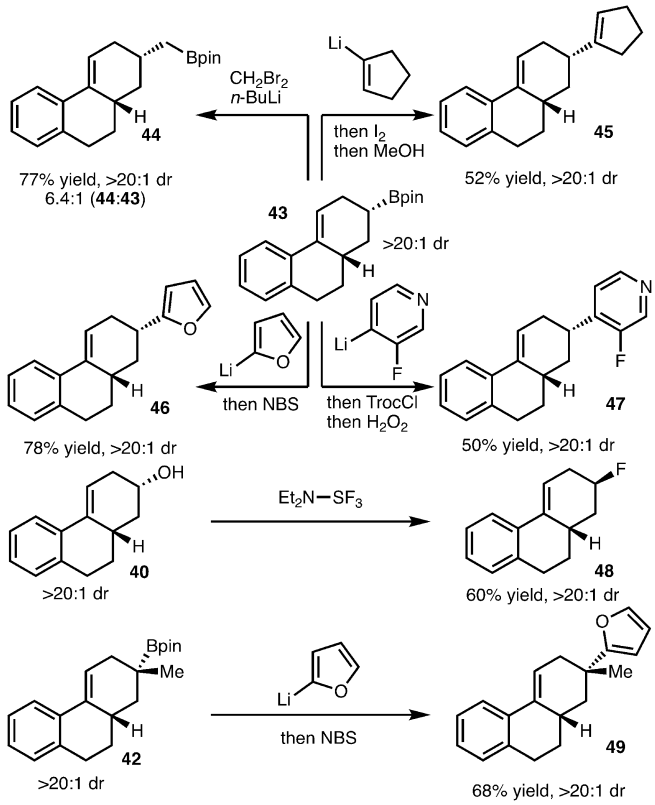
Due to the availability of the starting materials, the ease of the alkenylborane preparation, and the subsequent cycloaddition conditions, this approach was amenable to gram-scale synthesis (Scheme 7). Starting from 5.0 mmol of octahydrodindole **16**, cycloadducts **42** and **43** could be isolated with good yield and selectivity. In these cases, the reaction was treated with pinacol to provide direct access to the pinacolboronate ester. In addition, for larger scale operations, octahydroindole **16** could be recovered in 85% and 92% yield, respectively. Thus, while this process does use stoichio-




***Scheme 6.*** Cycloaddition with 1,2-disubstituted dienes.[21]




***Scheme 7.*** Preparative-scale reactions and synthesis of boronates.

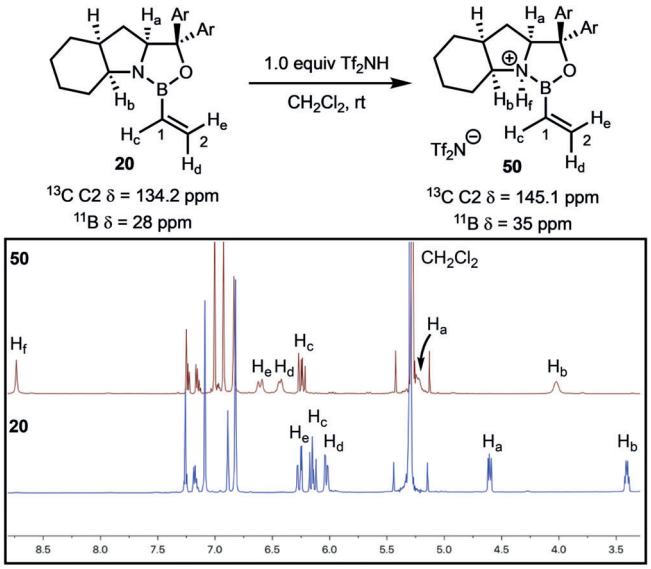



***Scheme 8.*** Transformations of products. See the Supporting Information for details.

metric quantities of a chiral component, it can be easily recycled.

Owing to the versatility of the C–B bond, the pinacolboronate ester products can be elaborated in various ways. In addition to the oxidative workups shown in Schemes 5–6 that led to formation of the corresponding alcohol, various C–C bond-forming processes were investigated. Starting from **43**, homologation (**44**),[13] olefination (**45**),[14] and arylation (**46** and **47**)[15,16] processes were achieved. In each case, the reactions were stereospecific since only a single diastereomer was observed. In addition, the derived secondary alcohol can also be used to generate secondary fluoride **48** with inversion of configuration.[17] The transformation of a Bpin-substituted quaternary carbon proved to be more difficult with established reaction methods. However, arylation with 2-lithiofuran did lead to the formation of **49** from **42**.[15] We expect that with additional innovations in the transformation of Bpin-substituted quaternary carbons, the utility of these products beyond oxidation and arylation will be improved.[10] Finally, it is important to note that all of the products illustrated in Scheme 8 would be challenging to prepare with traditional enantioselective [4+2]-cycloadditions. For example, enantioselective preparation of furan **49** would require extensive manipulation of the ester- or ketone-based products that are typically derived from known [4+2]-cycloadditions.

To provide support for the role of $Tf_2NH$ in this reaction, NMR analysis of the oxazaborolidine was carried out (Scheme 9). Upon treatment of **20** with 1.0 equiv of $Tf_2NH$, significant downfield shifts for many of the signals were




***Scheme 9.*** 1H NMR spectra of oxazaborolidine and N-protonated oxazaborolidine.

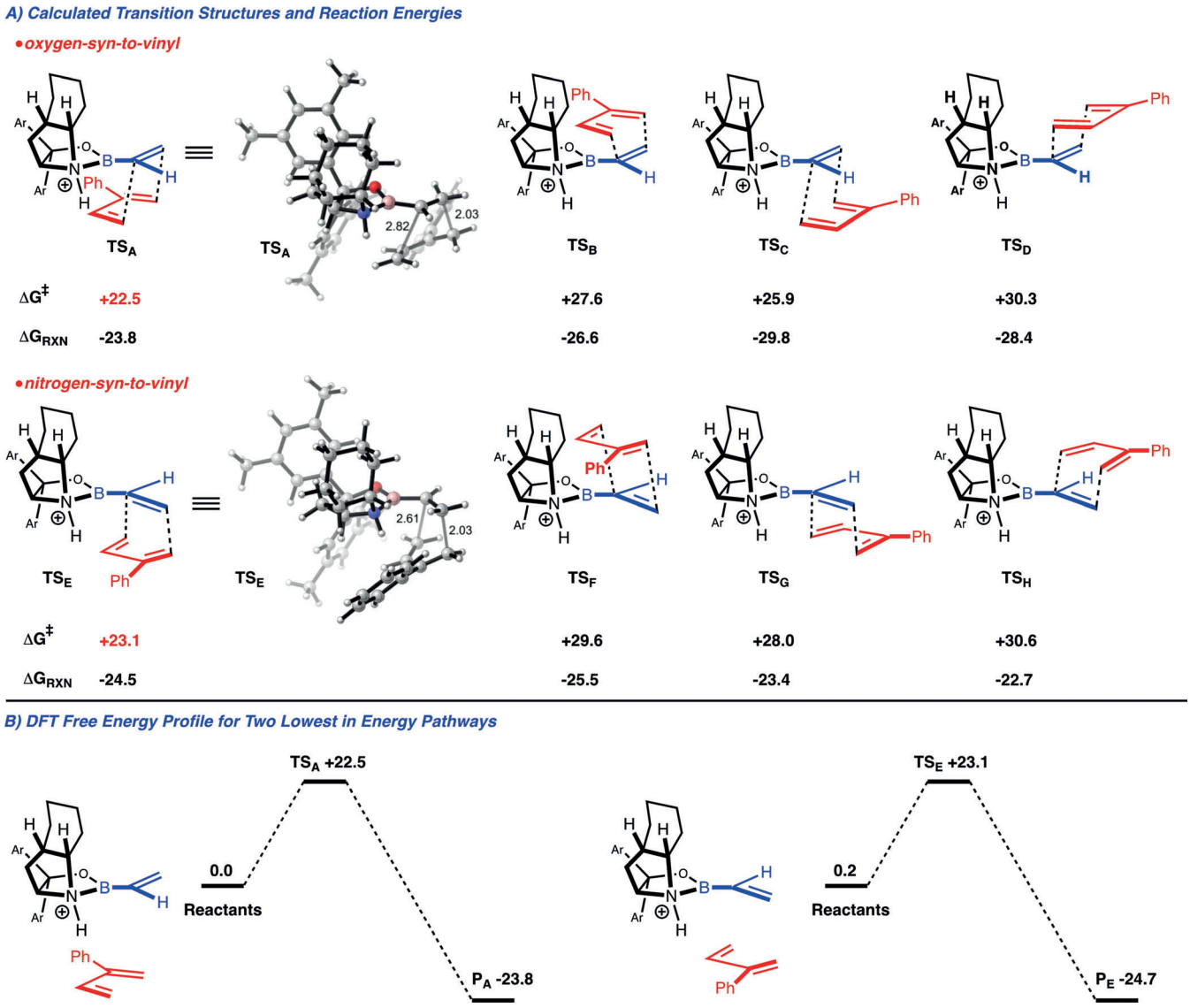



***Figure 1.*** DFT studies of the [4+2]-cycloaddition with the counterion omitted. Energies reported in kcal mol$^{-1}$, interatomic distances are in Ångströms.

observed in the $^1$H NMR spectrum, thus indicating the likely formation of **50**. In addition, downfield shift for the boron atom and the C2-alkene carbon (the C1 carbon of the alkene could not be detected by $^{13}$C NMR due to quadrupolar relaxation of the boron) were also observed. In particular, the resonances were shifted downfield, thus suggesting that protonation with $Tf_2NH$ decreases the electron density at these positions.

To probe the basis for the observed enantioselectivity, we investigated the energy landscape with density functional theory (DFT) calculations at the CPCM(dichloromethane)-ωB97X-D/def2-QZVPP//B3LYP/6-31G level of theory (see the Supporting Information).[18] There are four possible [4+2]-cycloaddition transition structures (TS) that lead to the observed regioisomer. In addition, the N-protonated alkenyl oxazaborolidine can adopt two conformations (*oxygen-syn-to-vinyl* and *nitrogen-syn-to-vinyl*). Thus, a total of eight TS structures were located for the [4+2] cycloaddition between chiral N-protonated alkenyl oxazaborolidine **20** and 2-phenyl butadiene. The computed potential energy profiles are summarized in Figure 1 A. For the *oxygen-syn-to-vinyl* TS conformers, the *endo* $\mathbf{TS_A}$ was the lowest in energy, which follows traditional [4+2]-cycloaddition *endo* paradigms and leads to formation of the observed enantiomer. $\mathbf{TS_E}$ is close in energy to $\mathbf{TS_A}$ ($\Delta\Delta G^{\ddagger} = 0.6$ kcal mol$^{-1}$), but leads to formation of the minor enantiomer (Figure 1 B).[19] Given the high levels of enantioselectivity observed in this reaction (99:1 er), a $\Delta\Delta G^{\ddagger}$ of at least 2.5 kcal mol$^{-1}$ would be expected. Therefore, a key aspect of the reaction that is crucial for selectivity must have been omitted from the model chosen for calculations.

The component of the reaction that was absent from the calculations was the counterion, bis(trifluoromethane)sulfonamide. To further explore the effects of the counterion on the stereoselectivity, we re-computed $\mathbf{TS_A}$ and $\mathbf{TS_E}$, but now in the presence of the counterion (Figure 2). In the case $\mathbf{TS_A}$-

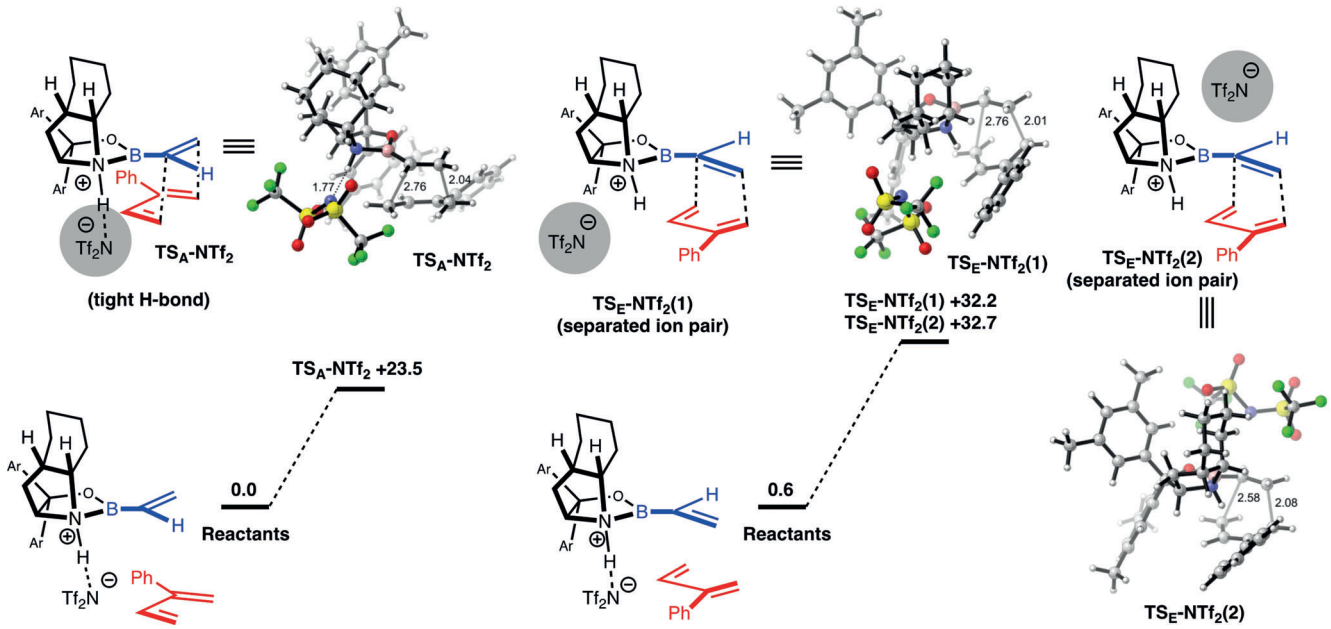



***Figure 2.*** DFT studies of the [4+2]-cycloaddition with the counterion included. Energies reported in kcal mol$^{-1}$, interatomic distances are in Ångströms.

$NTf_2$, the counterion optimizes close to the $HN^+$, forming a hydrogen-bonded tight-ion pair. In **TS$_E$**-$NTf_2$, the hydrogen-bonding and close association of the cation of N-protonated alkenyl oxazaborolidine **20** and the anion is unachievable due to steric pressure with the diene, and instead, conformations without $N^-$-$HN^+$ hydrogen bond have to be adopted. Therefore, the counterion was positioned at the most electropositive regions of **TS$_E$** with two different orientations, **TS$_E$**-$NTf_2$(1) and **TS$_E$**-$NTf_2$(2). Thus, **TS$_A$**-$NTf_2$ is substantially lower in energy ($\Delta\Delta G^{\ddagger} = 8.1$ kcal mol$^{-1}$ and 8.6 kcal mol$^{-1}$) than **TS$_E$**-$NTf_2$(1) and **TS$_E$**-$NTf_2$(2). The trend observed from these data shows that the strong association of the counterion with the TS structure greatly influences the stereoselectivity of the reaction.[20]

Based on the computed transition structures shown in Figure 2, we can confidently illustrate models to rationalize the observed selectivity for the other substrate classes (Figure 3). In the case of isopropenyl oxazaborolidine **18**, **TS$_I$** is likely operative. Regarding the reaction of cyclopentadiene with vinylborane **20**, *endo*-approach **TS$_J$** appears to be slightly favored (See Scheme 5, products **37a**,**b**). However, with isopropenyl borane **18**, the *exo*-approach **TS$_K$** is preferred (See Scheme 5, product **24**). It is likely that steric pressure between the methyl group of the alkenylborane and the methylene unit of cyclopentadiene disfavors the *endo* approach. The observations made here with cyclopentadiene and **20** are consistent with those made in related [4+2]-cycloadditions with 2-substituted acrolein derivatives.[3]

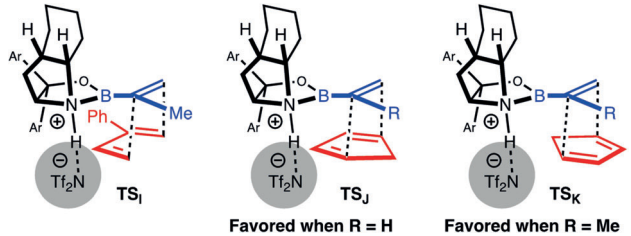



***Figure 3.*** Transition structures for other substrates classes.

## Conclusion

In conclusion, we have introduced a method that addresses the long-standing challenge of stereoselective [4+2]-cycloadditions with chiral alkenylboranes. This was achieved through the introduction of a new strategy that enables in situ generation of a highly reactive dienophile. The products of these reactions enable the formal synthesis of cycloadducts that would be challenging to access with existing [4+2]-cycloaddition strategies. In addition, mechanistic investigations uncovered a significant role of the counterion in influencing the conformation of the dienophile and the stereoselectivity of the reaction. Finally, the approach outlined here introduces a strategy that suggests that achiral oxazaborolidines in combination with chiral Brønsted acids could enable the development of catalytic enantioselective variants, and studies along these lines are currently under investigation.

## Acknowledgements

We thank Indiana University and a NSF CAREER award (CHE1554760) for financial support. This project was partially funded by the Vice Provost for Research through the Research Equipment Fund and the NSF (CHE1726633 and

1764328). Computations were performed on the Hoffman2 cluster at UCLA.

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** alkenylboranes · chiral auxiliaries · cycloaddition · dienes · synthetic methods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[20] While the tight hydrogen bond interaction in $\mathbf{TS_A}$-$NTf_2$ slightly raises the LUMO relative to conformations that lack a tight hydrogen bond, as is reflected in the 1 kcal mol$^{-1}$ higher

activation energy in the contact ion pair, the energy to separate the ions is much larger than this small increase in activation energy.

[21] CCDC 2001031 (**18**), 2001033 (**39**), and 2001034 (**40**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Manuscript received: January 14, 2020
Revised manuscript received: March 21, 2020
Version of record online: ■■ ■■, ■■■■

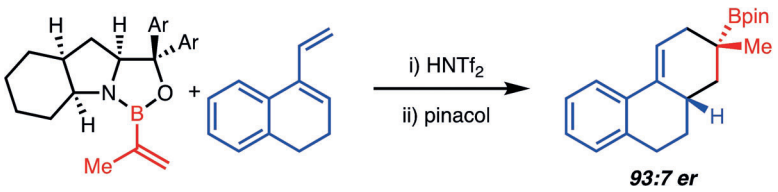
  

# Research Articles

**Cycloaddition**

D. Ni, B. P. Witherspoon, H. Zhang, C. Zhou, K. N. Houk,* M. K. Brown* _____ ■■■■–■■■■

Stereoselective [4+2]-Cycloaddition with Chiral Alkenylboranes




**Stereoselective [4+2]-cycloaddition** of alkenylboranes and dienes was accomplished through the introduction of chiral N-protonated alkenyl oxazaborolidines as dieneophiles. The reaction gives products that can be readily derivatized to more complex structural motifs through stereospecific transformations of the C–B bond such as oxidation and homologation. DFT calculations uncovered a surprising effect of the counterion on stereoselectivity.