Organic LETTERS

Letter

Cite This: Org. Lett. 2018, 20, 2649−2653

pubs.acs.org/OrgLett

Oxazaborinines from Vinylogous *N*-Allylic Amides: Reactivities of Underexplored Heterocyclic Building Blocks

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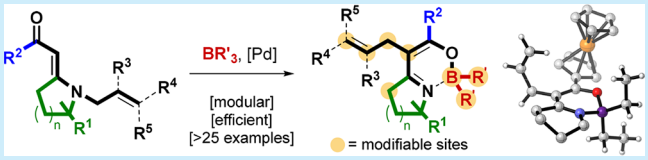
Supporting Information

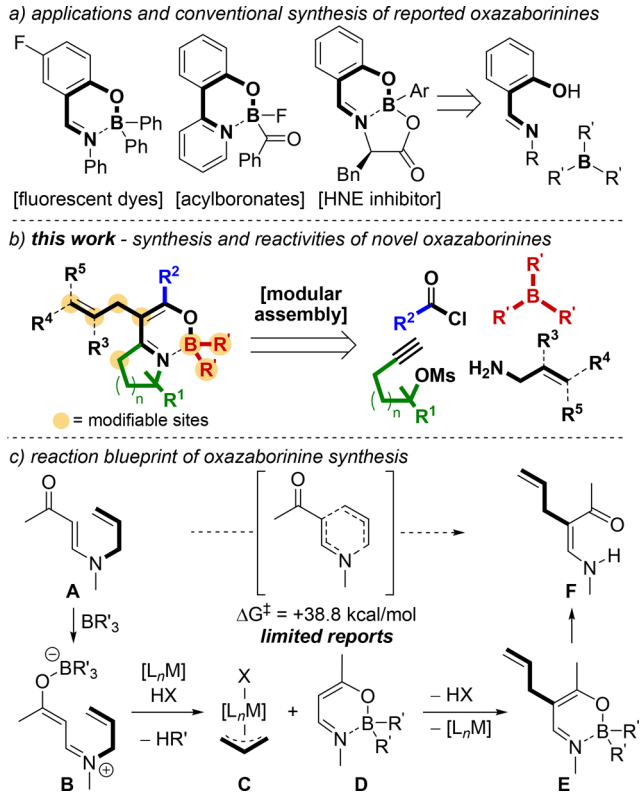
ABSTRACT: Access to a new class of oxazaborinines using an efficient transition-metal-catalyzed rearrangement is demonstrated. The method overcomes the synthetic challenge of achieving an aza-Claisen rearrangement of vinylogous *N*-allylic amide substrates, giving rise to a variety of highly modifiable oxazaborinine products. An investigation of the unique reactivity of these boron-based heterocycles has unveiled their underexplored potential as valuable building blocks and intermediates for organic synthesis.



Oxazaborinines represent an intriguing class of compounds with remarkable properties.[1] Considerable research has focused on their photophysical applications[2] and use as fluorescent dyes[3] or in bioimaging (Scheme 1a).[4] Unusual structural aspects of oxazaborinines[5] and investigations of *B*-chiral acylboronates have also emerged.[6] More recently, it has been discovered that molecules containing (anionic) tetrahedral boron have significant medicinal value,[7] such as HNE[8] or NLRP3 inflammasome inhibitory activity.[9] The vast majority of reported oxazaborinines are prepared by treatment of salicylaldimines with a borane to give boranils, which cannot be easily functionalized thereafter. Related congeners have also been synthesized from β-diketones by their condensation with a primary amine and subsequent reaction with a borane.[10] Notably, regioselectivity issues in the condensation step limits the use of the latter approach in the case of unsymmetrical β-diketone substrates. Despite numerous reports centered on the properties of oxazaborinine products, there is little insight into their stability, reactivity, and potential for use in *further synthetic transformations* once the boron has been installed. Intrigued by the underexplored reactivity of such boron-based heterocycles, we set out to investigate if oxazaborinines might serve as valuable structural motifs for organic synthesis. In this context, we also sought to develop a new method to access a wider class of oxazaborinines that could be assembled in a modular fashion and easily functionalized at a late stage (Scheme 1b).

We hypothesized that *N*-allylic vinylogous amides (enaminones) such as **A** (Scheme 1c) could be converted to substituted oxazaborinines of type **E** in one step using a hybrid process that combines reactions reminiscent of C−N activation[11] and transition-metal-catalyzed allylic alkylation of enolates.[12] As outlined in the reaction blueprint, activation of vinylogous amide **A** (e.g., with BR'_3) would first afford iminium-type intermediate **B**. In the presence of both a transition metal and Brønsted acid catalyst, oxidative addition would give rise to π-allyl complex **C** and enolate equivalent **D**. Allylic alkylation of the latter intermediate would then complete the catalytic cycle and furnish substituted oxazaborinine **E** as a formal [3,3] rearrangement product. While the combination of transition-metal catalysts and Brønsted and/or Lewis acid additives has found broad use in π-

Scheme 1. Introduction to Oxazaborinine Structures and Synthesis



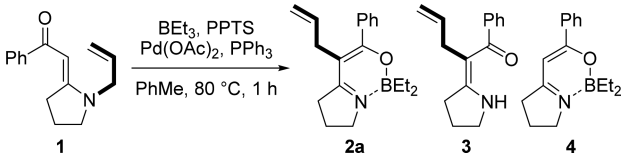
Received: March 16, 2018
Published: April 18, 2018

DOI: 10.1021/acs.orglett.8b00859
Org. Lett. 2018, 20, 2649−2653

allyl chemistry,[13] to the best of our knowledge, the application of oxazaborinines as nucleophiles is unprecedented in this context. If desired, **E** could also provide access to α-substituted enaminone **F** via hydrolysis. Vinylogous amides, such as **F**, combine the ambident nucleophilicity of enamines with the electrophilicity of enones and are valuable multipurpose building blocks for organic chemistry,[14] aza-heterocycle synthesis,[15] and pharmaceutical development.[16] It is noteworthy that the [3,3] sigmatropic rearrangement of *N*-allylic *enaminones* (**A**) to give, after tautomerization, products of type **F** has very limited literature precedent,[17] unlike the related aza-Claisen rearrangement involving *enamines*.[18,19] The activation barrier for the [3,3] sigmatropic rearrangement of **A** was calculated to be even higher compared to the classic aza-Claisen reaction,[20] likely due to the additional penalty imposed by breaking the *enaminone* conjugation. Notably, the aza-Claisen rearrangement of **A** cannot be achieved by only taking advantage of charge-acceleration of this rearrangement,[19b] since vinylogous amides are not *N*-nucleophilic.[21]

We commenced our investigation with vinylogous amide **1** as the substrate (Table 1). Simply heating a solution of **1** in *o*-dichlorobenzene to above 220 °C did not lead to formation of rearrangement product **3** but, rather, gradual decomposition of the starting material, consistent with the calculated high activation barrier for the [3,3] sigmatropic rearrangement of vinylogous amides.[22] We ultimately found that a formal aza-Claisen rearrangement with concomitant oxazaborinine formation occurred smoothly by using the specific combination of triethylborane, palladium(II) acetate, triphenylphosphine, and pyridinium *p*-toluenesulfonate to yield oxazaborinine **2a** in 95% isolated yield (entry 1). Deallyl oxazaborinine **4** was formed as the sole identifiable side product in trace quantities under these reaction conditions. The undesired formation of **4** was generally found to be more pronounced in substrates bearing substituted allylic groups (vide infra). Several control experiments corroborate the proposed reaction mechanism illustrated in Scheme 1c and highlight the necessity of the palladium catalyst and Brønsted acid additive as well as discount the possibility of the transformation being solely acid catalyzed (entries 2–4).

Table 1. Reaction Development and Control Experiments



entry	variation from above	conv of **1**[a] (%)	yield[a] (%) **2a**	**3**	**4**
1	none[b]	>98	95[c]		tr
2	no $Pd(OAc)_2$ and PPh_3	<5			
3	no PPTS	<5			
4	only PPTS	<5			
5	no BEt_3	>98		57[c]	
6	23 °C, 12 h	>98	80		tr
7	TFA instead of PPTS	>98	88		10
8	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	>98	67	14	tr

[a]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Conditions: BEt_3 (1.5 equiv), PPTS (10 mol %), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), PhMe, 80 °C. [c]Isolated yield.

While the formal aza-Claisen reaction could also be conducted without triethylborane, the isolated yield of the rearranged product (**3**) was mediocre (57%, entry 5). Oxazaborinine **2a** also formed at room temperature upon extended reaction times (entry 6). Notably, other Brønsted acid additives or palladium sources gave inferior results (entries 7 and 8). Moreover, a crossover experiment corroborated the proposal that the reaction proceeds via a π-allyl palladium complex (**C**, Scheme 1c) that is dissociated from the parent vinylogous amide and leads to *intermolecular* allylic alkylation.[23]

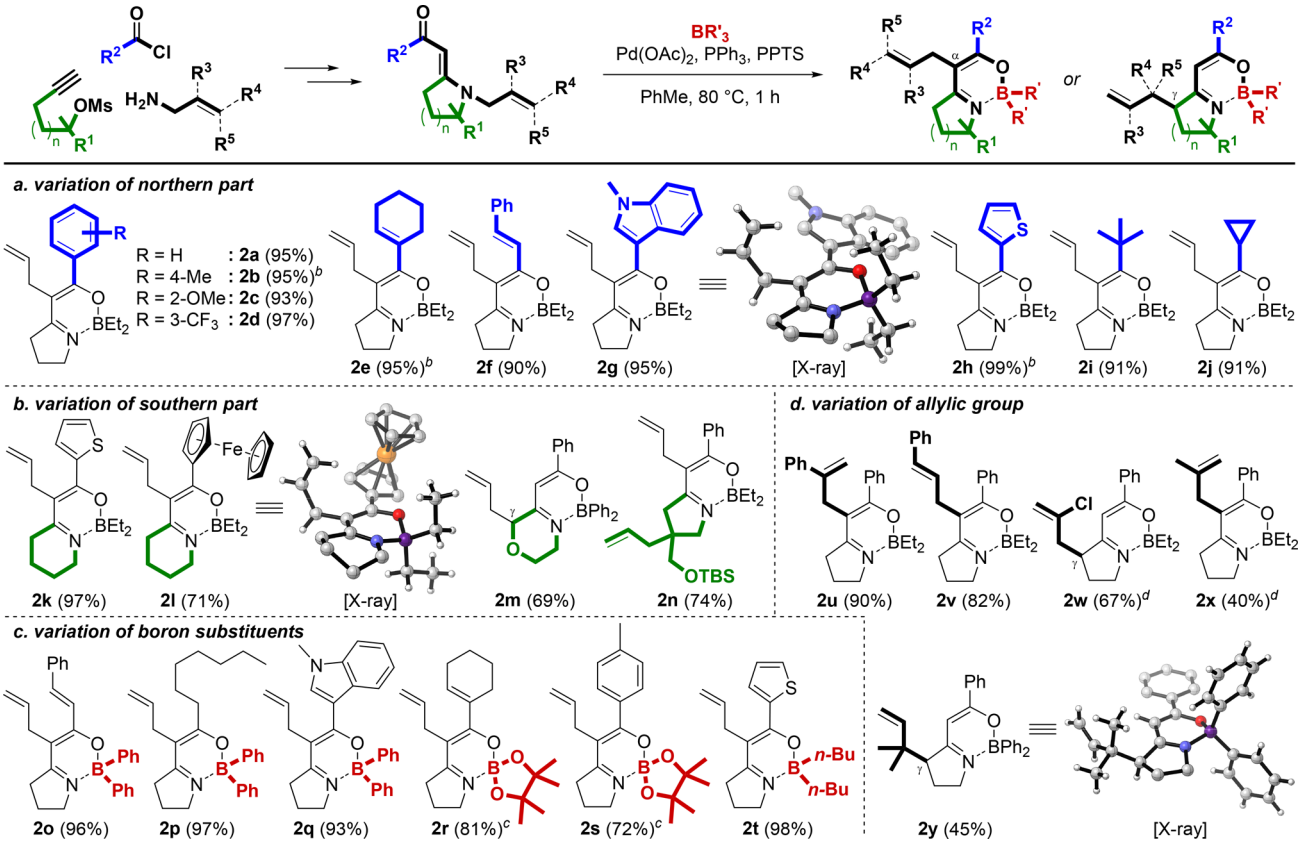
With the optimized conditions in hand, the scope of this Pd-catalyzed oxazaborinine synthesis was investigated (Scheme 2). Vinylogous amide substrates with varied substitution patterns were generated through sequential Sonogashira coupling of alkyne mesylates with acid chlorides, followed by conjugate addition/displacement with allylic amines.[23] The identity of R^2 has little influence on the reaction outcome, and oxazaborinines with aromatic, olefinic, heterocyclic, or aliphatic appendages were all formed in >90% yield (**2a–j**, Scheme 2a). This method proved robust and just as efficient on a >2 mmol scale (**2b**, **2e**, and **2h**). As shown in Scheme 2b, the established reaction conditions were also applicable for the efficient preparation of oxazaborinines **2k–n**. The structure of the ferrocenyl derivative **2l** (mp 108–113 °C) was unambiguously confirmed by single-crystal X-ray analysis. The modularity of our oxazaborinine synthesis made it possible to readily replace triethylborane with other boron reagents to give diphenyl, pinacol, or di-*n*-butyl derivatives (**2o–t**, Scheme 2c). Finally, submitting vinylogous amides bearing substituted allylic groups to the Pd-catalyzed rearrangement conditions (Scheme 2d) gave products such as phenallyl **2u** and cinnamyl oxazaborinine **2v** in high yields under the standard reaction conditions, whereas chloroallyl derivative **2w** required more forcing conditions (111 °C). Alkyl substituents on the allyl group (i.e., methallyl or prenyl) were not as well tolerated in the reaction, providing products **2x** and **2y** in diminished yields.[24] It is interesting to note that oxazaborinines **2m**, **2w**, and **2y** bear the allylic group at the γ-position, unlike all other cases where α-allylated products are formed. A full understanding of the factors that lead to this selectivity remains a matter of ongoing investigation.[25]

As shown in Scheme 3, upon subjecting isomeric vinylogous amide substrates **5** and **6** to the established Pd-catalyzed conditions, the *α-linear* oxazaborinine **2v** was exclusively formed, irrespective of the vinylogous amide starting material. Alternatively, Ru-catalyzed transformation converted **6** to the *α-branched* oxazaborinine **8** as the major product, along with a minor amount of **2v** (18%) and deallyl derivative **4** (19%). Interestingly, Ir-catalyzed transformation of **5**[26] yielded *γ-branched* oxazaborinine **7** in 62% yield.[27] While traces of the *α-branched* oxazaborinine **8** were detected in the crude reaction mixture, this reaction outcome is especially impressive since **7** was formed as a single diastereomer.[28]

Given the uniqueness of the oxazaborinine products, we have also investigated their reactivity in further synthetic transformations. In general, the oxazaborinine moiety is stable toward many reaction conditions, and could in principle function as a "protecting group" for the vinylogous amide, whose stability can be fine-tuned by choice of the boron substituents. As such, hydrogenation or oxidation of the allyl group (Scheme 4) gave rise to the corresponding products **9** and **10** in good yields, leaving the oxazaborinine core unaffected. Treatment of oxazaborinine **2h** with a mixture of [bis(trifluoroacetoxy)iodo]-benzene and trimethylsilyl chloride leads to a clean *α*-

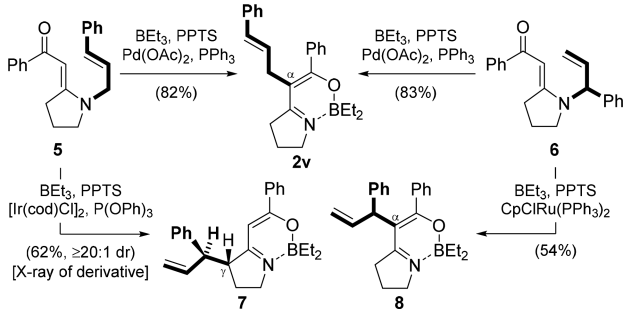
DOI: 10.1021/acs.orglett.8b00859
Org. Lett. 2018, 20, 2649–2653

Scheme 2. Scope of Modular Oxazaborinines[a]

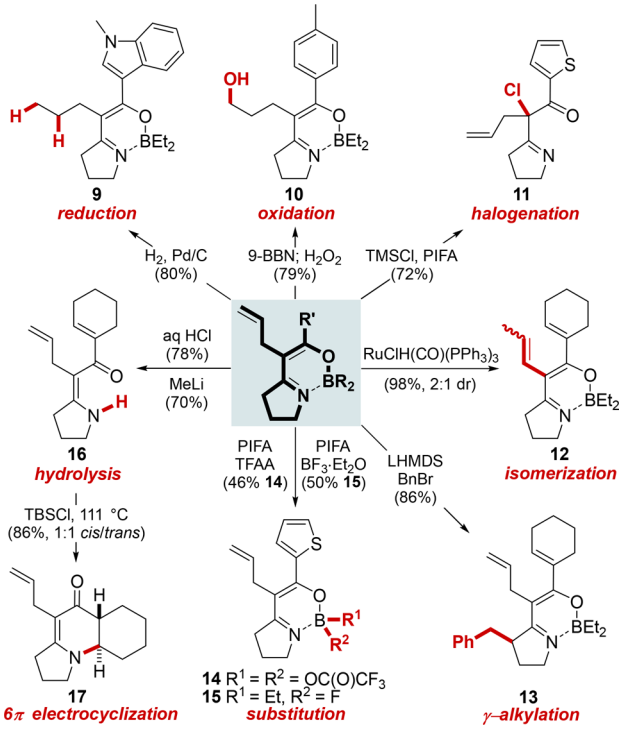


[a]Yields of isolated products after purification by flash chromatography on silica gel. [b]Reaction conducted on >2 mmol scale. [c]MeO-Bpin (methoxyboronic acid pinacol ester) was employed as BR′3. [d]Reaction conducted at 111 °C.

Scheme 3. Catalyst-Dependent *Linear* vs *Branched* Selectivity



Scheme 4. Derivatizations of Oxazaborinines



halogenation, giving chloroimine **11**, which features a fully substituted carbon center. An Ru-catalyzed olefin isomerization[29] smoothly formed **12**, and deprotonation of **2e** and trapping with benzyl bromide afforded γ-alkylated oxazaborinine **13**. The substituents on boron can also be exchanged, affording bis-trifluoroacetate **14** and fluoro oxazaborinines **15**, respectively. The latter product is worth noting since it is a unique *B*-chiral molecule.[6,30] While the (diethyl) oxazaborinine moiety of **2e** proved remarkably resistant toward aqueous acidic or basic conditions and even strong hydridic reducing agents (excess lithium aluminum hydride at 66 °C), pinacol congener **2r** was readily hydrolyzed with dilute aqueous acid to afford vinylogous amide **16** in 78% yield. Hydrolysis of diethyl oxazaborinines, such as **2e**, can also be achieved by treatment with methyllithium. Vinylogous amide **16** underwent 6π electrocyclization at elevated temperature to give tricycle **17**, which features a natural product-like scaffold.[31]

DOI: 10.1021/acs.orglett.8b00859
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In summary, we report a modular and highly efficient transition-metal-catalyzed strategy to access oxazaborinines starting from vinylogous *N*-allylic amides. The unusual reactivity of the oxazaborinines highlights their untapped potential as valuable building blocks and intermediates for organic synthesis, thus extending their previous application in research areas ranging from materials chemistry to pharmaceutical development. Our successful implementation of a variant of the transformation using an iridium-based catalyst sets the stage for the development of an asymmetric version. Studies in this direction and demonstrating the utility of oxazaborinines in the total synthesis of complex natural products are the focus of our current efforts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00859.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 1815588−1815591 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.L.H. is thankful for a postdoctoral scholarship from the Swiss National Science Foundation. We thank Dr. Kevin Kou (UC Berkeley) for assistance with DFT computations, Nicholas Settineri (UC Berkeley) for single-crystal X-ray diffraction studies, and Yannick Linne (Leibniz Universität Hannover) for a gram-scale preparation of amide **1**. Portions of this work are supported by a grant from the American Chemical Society Petroleum Research Fund to R.S. (ACS-PRF No. 43546-G1).

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DOI: 10.1021/acs.orglett.8b00859
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(20) The calculated $\Delta G^{\ddagger}$ values of the aza-Claisen rearrangement and the [3,3] rearrangement of *N*-allylic enaminones are significantly higher compared to the classic Claisen rearrangement (roughly 7 $^{kcal}/_{mol}$ and 11 $^{kcal}/_{mol}$, respectively). A comparison of calculated $\Delta G^{\ddagger}$ values (at B3LYP/6-31+G(d,p) level of theory, using Gaussian16) for all these related rearrangements is presented in the Supporting Information.

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(22) The calculated activation barrier for the aza-Claisen rearrangement of **1** ($\Delta G^{\ddagger}$ = +39.0 kcal/mol) is similar to that of **A**.

(23) See the Supporting Information for experimental details.

(24) Deallyl oxazaborinine **4** was found to be a significant side product generated in these reactions.

(25) Preliminary studies indicate a circumstance more complex than oxazaborinines undergoing imine−enamine-like tautomerism, allowing the α-allylic products to convert to γ-derivatives via a Cope rearrangement.

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DOI: 10.1021/acs.orglett.8b00859
Org. Lett. 2018, 20, 2649−2653