Introducing Alkene Moieties via Iterative Carbenoid Insertions: Vinylene Homologation of Organoboronates

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ABSTRACT: The Matteson homologation of organoboronates has been an attractive approach for constructing aliphatic carbon chains via iterative insertion of carbenoids. However, the corresponding homologation that can introduce alkene moieties to molecular backbones remains elusive. Here we report the development of a stereoselective vinylene homologation of various alkyl and aryl boronates. The reaction is enabled by diastereoselective consecutive insertion of a silyl- and an alkoxy-substituted carbenoid, followed by a Peterson-type elimination. Diverse alkenyl boronates can be obtained in good yield and good to excellent *trans* selectivity. Density functional theory (DFT) calculations revealed the origin of diastereoselectivity in carbenoid insertion and how Lewis acids with different sulfide binding affinities affect the competing S_N2- and S_N1-type 1,2-boronate migration pathways with distinct levels of stereospecificity. This protocol has been successfully applied to programmable synthesis of piperamide-family natural products by merging with the methylene homologation. Guided by the mechanistic understanding, preliminary success has been achieved with the *cis*-selective vinylene homologation enabled by oxyphilic Lewis acids.

INTRODUCTION

Homologation reactions have been broadly useful in organic synthesis, as it enables direct editing of molecular scaffolds via either chain elongation or ring expansion without altering the original reacting group.[1] In particular, the boron-based homologation, namely the Matteson-type reactions, has become increasingly important to the development of programmable or automated organic synthesis through precise control of the addition sequence and stereochemistry.[2,3] In a typical Matteson reaction, carbenoids are inserted into C−B bonds of boronates in an iterative manner (Scheme 1A), which introduces sp^3-hybridized carbons into the molecular backbone. Substantial hurdles remain for extending the Matteson homologation to construct diverse organic molecules. For instance, besides sp^3-carbons, heteroatoms and unsaturated moieties widely exist in molecular skeletons. Recently, we have developed the aza- and oxa-Matteson reactions to allow nitrogen and oxygen, respectively, to be installed during the chain propagation.[(4)] Considering that sp^2-carbons, in particular alkenes, frequently exist in scaffolds of functional organic molecules (Scheme 1B), the realization of stereoselective vinylene insertion into C−B bonds would be critical for introducing alkene moieties by this iterative boron homologation strategy.

Currently, a number of efficient methods exist for preparing alkenyl boronates, including alkyne hydroboration, bora-Wittig, Heck reaction, cross metathesis, and others.[5] However, synthesis starting from organoboronates has been rarely explored. The use of a bifunctional building block containing a boron-protecting group, e.g., (2-halo)-vinyl-*N*-methyliminodiacetic acid boronates, could result in a formal alkene insertion via the Pd-catalyzed Suzuki coupling.[6] While effective, this approach requires boron protection and deprotection, and the cross coupling with alkyl boronates is not a trivial issue.[6c] On the other hand, Zweifel Olefination is an elegant approach to couple an alkenyl group to a C−B bond; but the original boronate group is eliminated during this process (Scheme 1C).[7]

Considering the difficulty of directly inserting an alkene moiety into C−B bonds[8], we hypothesized that one approach could be to introduce two sp^3-carbon units consecutively, with each bearing a specific functional group (FG), and then allow these FGs to react and eliminate together under a specific condition (without affecting the boron group) to reveal the alkene moiety. As such, the overall transformation furnishes the vinylene homologation (Scheme 1D). While a number of olefination reactions could potentially be suitable for the proposed alkene-insertion strategy, our first-generation approach was inspired by the Peterson olefination because of the relative robustness of silane and ether moieties under the boron homologation (nucleophilic and basic) conditions.[9] We envisioned that sequential addition of silyl-[10] and alkoxy-substituted[11] methylene (or vice versa) into boronates, followed by in situ stereospecific elimination, should lead to the desired vinylene homologation product. However, a number of difficulties could be associated with this approach. First, in the final elimination step the *E/Z* selectivity of the olefin product would largely rely on the diastereopurity of the β-alkoxysilane intermediate; but there has been nearly no precedent to control diastereoselectivity of consecutive carbenoid insertions without using enantiopure reagents.[12] Thus, judicious choice of the silyl- and alkoxy-substituted carbenoid reagents would be highly important. In addition, direct homologation using oxy-bearing carbenoids has been much less developed than the carbon-substituted ones,[11] as oxygen can also serve as a good leaving group (LG) in Matteson-type reactions.[13] Moreover, compatibility of the boronate moiety under the Peterson elimination conditions could be another concern. In this full article, we describe the first development of stereoselective vinylene homologation of alkyl and aryl boronates via sequential and diastereoselective insertion of silyl- and alkoxy-substituted carbenoids, which provides a "boron-to-boron (B-to-B)" transformation without using protecting groups or noble metal catalysts.

Scheme 1. Vinylene Homologation and Strategy Design

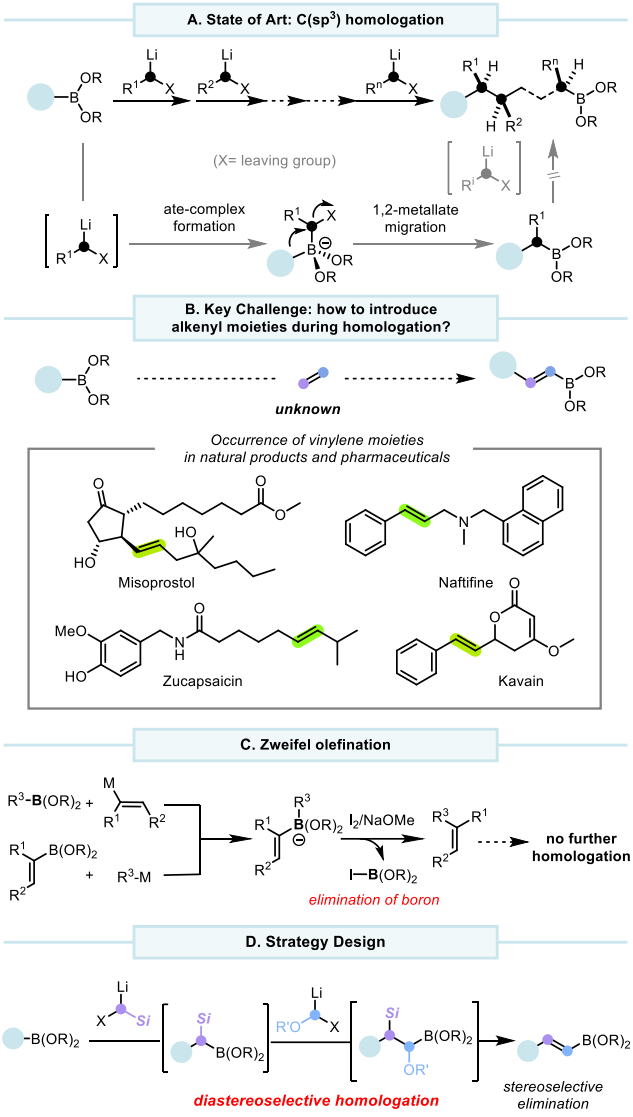
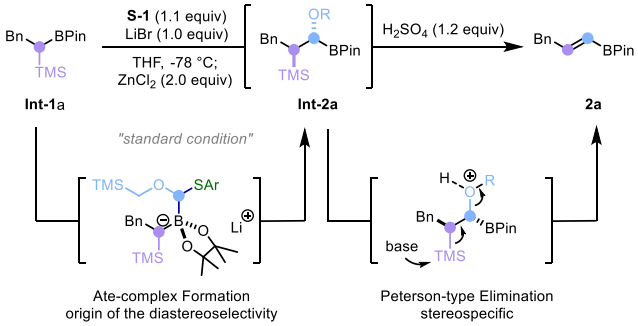
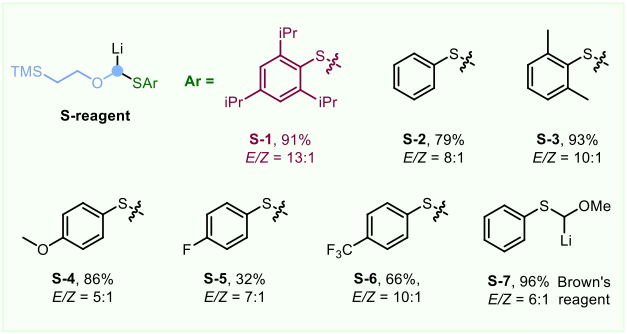


Table 1. Model Study to Access E-Alkenyl Boronates[a]



entry	variation from the standard condition	yield	*E/Z*
1	**none**	**91%**	**13 : 1**
2	**S-2 to S-7** instead of **S-1**	see below	
3	$HgCl_2$ instead of $ZnCl_2$	70%	2 : 1
4	w/o $ZnCl_2$	N.D.	-
5	$ZnCl_2$ was added at rt	90%	4 : 1
6	w/o LiBr	32%	2 :1
7	TsOH•H_2O (2.5 equiv)	93%	12 :1



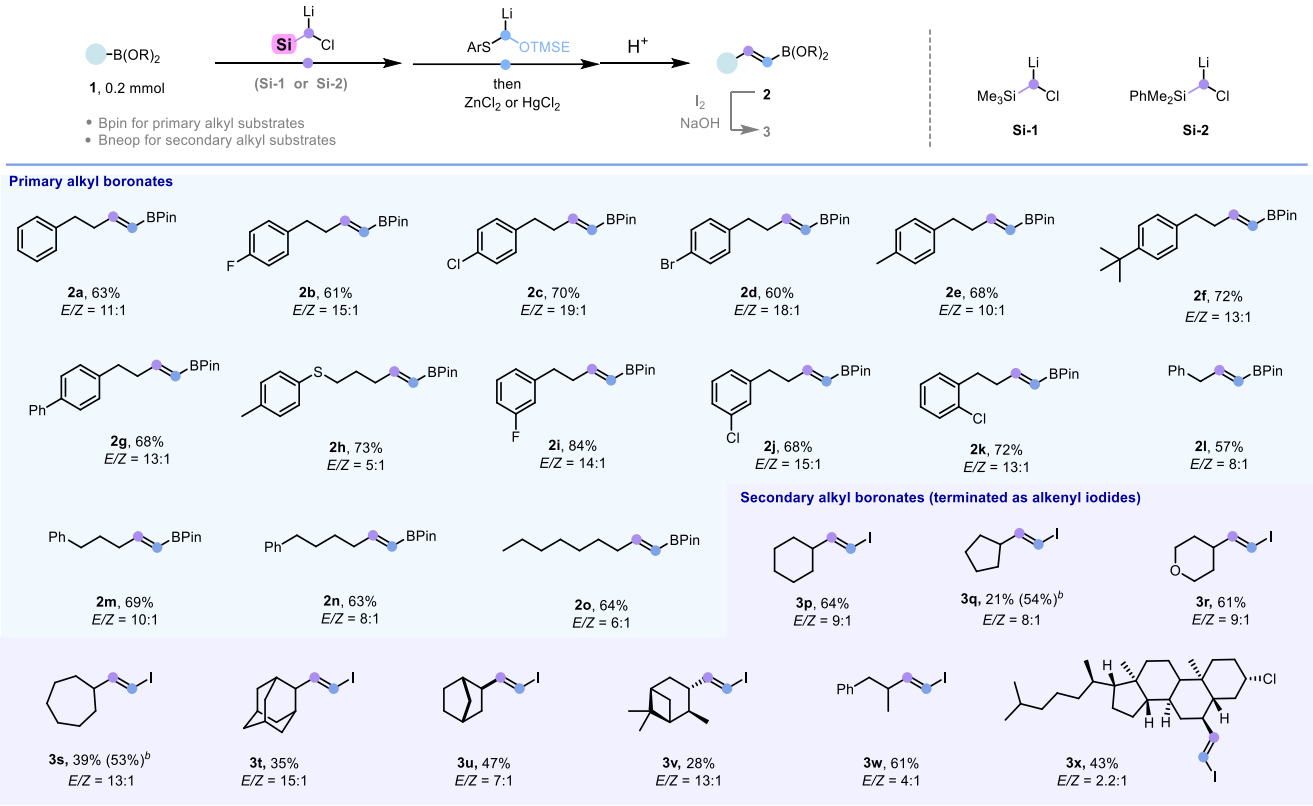
[a]Reaction conditions: **Int-1a** (0.1 mmol, 1.0 equiv), **S-reagent** (1.1 equiv), THF (1.0 mL), −78°C, 1 h; $ZnCl_2$ (2.0 equiv), 12 h; H_2SO_4 (1.2 equiv), 3h. Yields were determined by ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

RESULTS AND DISCUSSION

Given that consecutive insertions of heteroatom-substituted methylenes into boronates has been rare, our initial investigation was focused on the efficiency and diastereoselectivity of the insertion of alkoxy-substituted carbenoids into α-silylalkyl boronates. At the outset, pinacol boronate **Int-1a** was employed as the model substrate (Table 1). It can be envisioned that nature of the LG on the alkoxy-substituted carbenoid could have a profound impact on the reaction diastereoselectivity. Inspired by the earlier study of Brown,[11] various lithiated alkoxy aryl sulfanes (**S-reagent**), which were readily prepared from commercially available aryl thiols and 2-(trimethylsilyl)-ethoxymethyl chloride, were used as the precursors of the oxygen-substituted carbenoids. After forming an ate-complex intermediate, subsequent addition of a Lewis acid promoted the 1,2-metallate migration and allowed insertion of the oxygen-substituted methylene into the C−B bond. Our further study shows that simple one-pot treatment of the resulting α-alkoxy-β-silyl boronate intermediate with 1.2 equivalent of H_2SO_4 at room temperature afforded the desired alkenyl boronate product. Under the optimized conditions, a bulky arylthiolate LG was found to give high diastereoselectivity. When the 2,4,6-triisopropylphenyl-based S-reagent (**S-1**) was used, 91% yield and 13:1 *E/Z* selectivity were obtained (entry 1). Other aryl-substituted reagents with different steric and electronic properties all gave lower yield and/or lower diastereoselectivity (entry 2). $ZnCl_2$ proved be a more effective Lewis acid than $HgCl_2$ in this case (entry 3), and the ate-complex was stable and unactive when no Lewis acid was added (entry 4). When warming the reaction mixture to room temperature before adding $ZnCl_2$, the reaction proceeded in high yield but low *E/Z* selectivity (entry 5). Finally, the addition of LiBr can promote both the yield and diastereoselectivity (entry 6), though the exact reason remains to be determined. Comparable results were obtained using TsOH (2.5 equiv) instead of H_2SO_4 in the elimination step (entry 7).

With the optimized diastereoselective insertion and elimination conditions in hand, the direct vinylene homologation of alkyl boronates was explored (Table 2). The insertion of silyl-substituted carbenoids was carried out by adding the boronates to freshly prepared chloro(trimethylsilyl)-methyllithium (**Si-1**). The subsequent insertion of alkoxy-substituted carbenoids and acid-mediated elimination proceeded smoothly to deliver the

Table 2. Substrate Scope for Alkyl Boronates[a]

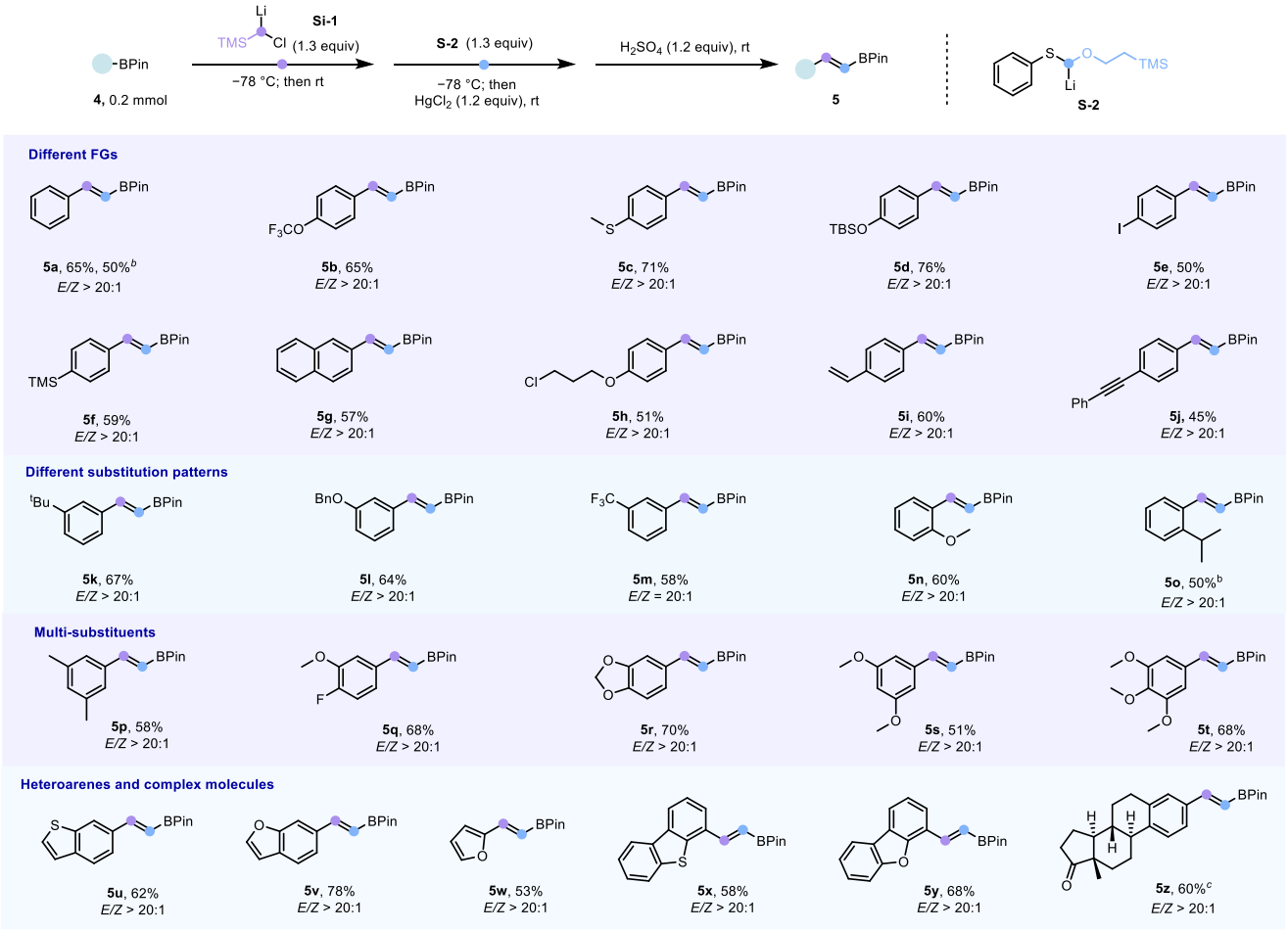


[a]All reactions were carried out on 0.2 mmol. For primary alkyl substrates, chloro(trimethylsilyl)-methyllithium (**Si-1**, 1.3 equiv), lithiated **S-1** (1.3 equiv), and $ZnCl_2$ (2.0 equiv) were used. For secondary alkyl substrates, chloro(dimethylphenylsilyl)-methyllithium (**Si-2**, 1.3 equiv), lithiated **S-2** (1.2 equiv), and $HgCl_2$ (1.2 equiv) were used. For experimental details, see the Supporting Information. Isolated yields are the overall yields of all operations starting from RBpin or RBneop. [b]The number in parenthesis is the NMR yield. The lower isolated yield is due to volatility of the products.

alkenyl boronate products without isolation of any reaction intermediates. Note that the addition of LiBr was not necessary during the insertion of alkoxy carbenoid as stoichiometric LiCl was generated after the silyl carbenoid insertion. The reaction shows a broad scope and various alkyl boronates underwent the vinylene homologation with good to excellent *E/Z* selectivity (up to 19:1).[14] FGs, such as aryl fluoride (**2b**, **2i**), aryl chloride (**2c**, **2j**, **2k**), aryl bromide (**2d**) and thioether (**2h**), were tolerated. When secondary alkyl boronates were used as substrates, the desired *E* alkene products were only observed in low yield under the standard conditions likely due to increased sterics. We hypothesized that the reactivity could be restored by reducing the steric congestion around the boron. Indeed, using the corresponding neopentyl glycol-derived boronates (Bneop), the reactivity was greatly improved. Meanwhile, employment of a bulkier dimethylphenylsilyl-derived carbenoid afforded better diastereoselectivity, and the use of $HgCl_2$ further improved the E/Z selectivity to some extent (see Supporting Information, Table S3). To ease the isolation process, the alkenyl Bneop products were directly converted to the corresponding alkenyl iodides. Cycloalkyl boronates of different ring sizes all showed moderate to good efficiency and good *E/Z* selectivity (**3p**-**3s**). Bridged-ring scaffolds (**3t** and **3u**) were compatible, and the acyclic secondary alkyl boronate (**3w**) also worked reasonably well. Moreover, the substrates derived from more complex natural products could deliver the desired vinylene homologation products (**3v** and **3x**) with retention of the relative stereochemistry.

Aryl boronates are also suitable substrates for vinylene homologation (Table 3). The use of $HgCl_2$ as the Lewis acid gave high diastereoselectivity during the alkoxy-carbenoid insertion (see Supporting Information, Table S4).[15] The reaction appears to be quite general. First, aryl groups with various substitution patterns, such as those containing para, ortho, or meta substituents, all afforded the desired products. The electronic properties of the arene do not seem to have a significant effect on either the reactivity or the *E/Z* selectivity. Unlike the cases of alkyl boronates, typically more than 20:1 *E/Z* selectivity were achieved for all the products. In addition, FGs, including trifluoromethyl ether (**5b**), thioether (**5c**), silyl ether (**5d**), iodide (**5e**), silane (**5f**) and alkyl chloride (**5h**), were compatible. Note that alkene (**5i**) and alkyne (**5j**) moieties were also tolerated. Moreover, heteroarene-derived boronates are competent substrates (**5u**-**5y**). This method can be used to derivatize an estrone-based substrate (**5z**). Finally, the reaction is scalable, and on 5 mmol scale alkenyl boronate product **5a** was isolated in 50% overall yield.

Table 3. Substrate Scope for Aryl Boronates[a]



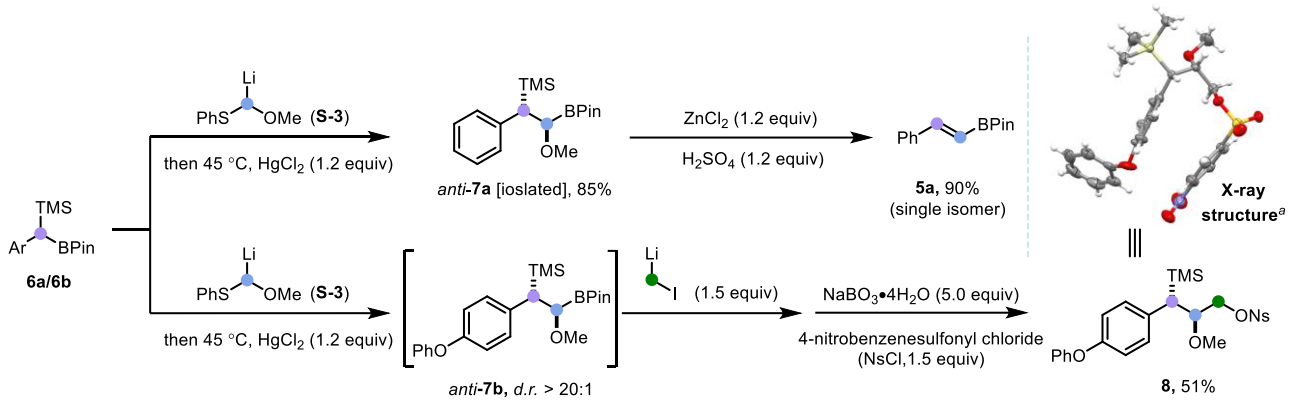
[a]All reactions were run on 0.2 mmol, unless noted otherwise. Isolated yields are the overall yields of all operations starting from RBpin. [b]Isolated yield on 5.0 mmol scale. [c]The corresponding ethylene glycol ketal was used as the substrate; H_2SO_4 (2.0 equiv) was added in the elimination step to reveal the ketone moiety through deprotection.

The reaction mechanism was explored through a combined effort between experiment and computation. The α-methoxy, β-silyl boronate intermediate (*anti*-**7a**) can be successfully isolated and characterized spectroscopically (Scheme 2). Its further treatment with acids delivered the *E* product **5a** exclusively, which confirms its intermediacy in the Peterson-type elimination step. To unambiguously determine the relative stereochemistry, further methylene homologation of the α-methoxy, β-silyl boronate intermediate (*anti*-**7b**) followed by oxidation and *p*-nosyl protection afforded sulfinate **8**, which can be characterized by X-ray crystallography. The X-ray structure of compound **8** clearly shows an *anti*-relationship between the silyl and the methoxy groups.

Density function theory (DFT) calculations were carried out to investigate the diastereoselectivity of the carbenoid insertion step and the Lewis acid effect. One intriguing question is whether the use of different Lewis acids ($ZnCl_2$ and $HgCl_2$) would alter the mechanism of the 1,2-boronate migration from a concerted S_N2-type pathway to a non-stereospecific stepwise S_N1-type pathway. First, the transition states of the addition of alkoxy-substituted carbanion **11** to *α*-silylalkyl boronate **10** was computed (Figure 1).[16] We hypothesize that the bulkiest silyl group should orientate nearly perpendicularly to the boronate plane but opposite to the direction of the carbenoid addition, which is analogous to both the Felkin−Anh and Cieplak models in carbonyl addition reactions.[17] The calculated transition states corroborate this hypothesis. Our computation indicates that boronate **12a** is the kinetically favored product, which is formed through transition state **TS1a**. In contrast, transition state **TS1b** leading to the other diastereomer **12b** is 1.3 kcal/mol less stable than **TS1a**, due to unfavorable gauche-like interactions between the arylthiolate LG and the α-methyl group on boronate **10**.[18] This stereochemical model is also consistent with the higher diastereoselectivity observed with bulkier arylthiolates (e.g., **S-1**, Table 1).

Next, we considered the $ZnCl_2$-promoted 1,2-migration from boronate **12a**. Conformational sampling using CREST and DFT calculations (see Supporting Information for details) suggests that $ZnCl_2$ prefers to bind to the arylthiolate sulfur and one of the boronate oxygen atoms to form **13a** (Figure 2). From **13a**, the S_N2-type pathway, where the 1,2-migration and arylthiolate LG dissociation occur via a concerted transition state **TS2** was found to be the most favorable with an activation free energy ($\Delta G^{\ddagger}$) of 15.6 kcal/mol. By contrast, the S_N1-type pathway that involves a stepwise LG dissociation to form **14** followed by 1,2-migration via either **TS3a** or **TS3b** is less favorable because the

Scheme 2. Intermediate Isolation and Relative Stereochemistry



[a]Thermal ellipsoids are displayed at 50% probability.

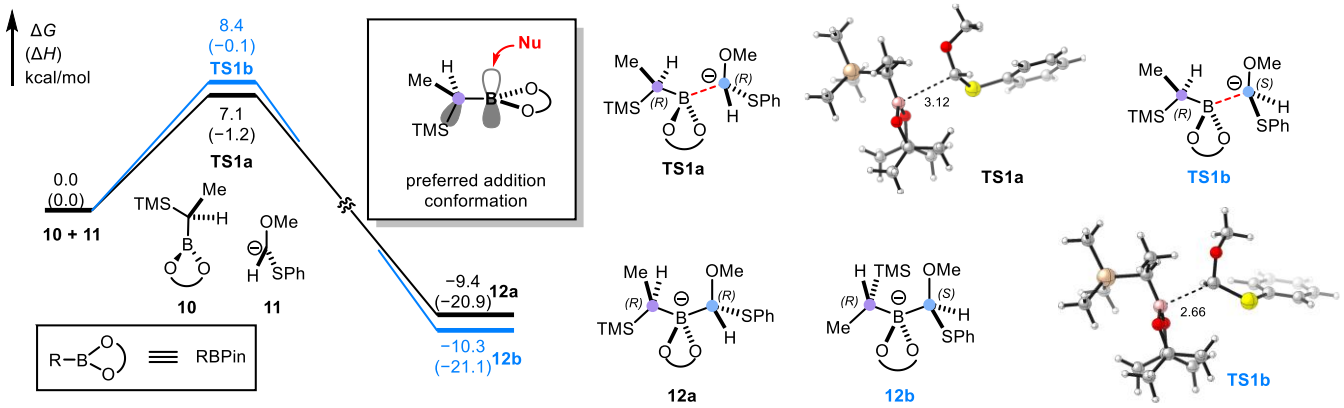


Figure 1. Computed energy profile of the diastereoselective carbenoid addition to α-silylalkyl boronate **10**. All the boronates used were pinacol boronic esters. DFT calculations were performed at the M06/6-311+G(d,p)/SMD (THF)//B3LYP-D3(BJ)/6-31G(d)/SMD(THF) level of theory. Conformational sampling was performed with CREST at the GFN-xTB2 level of theory.

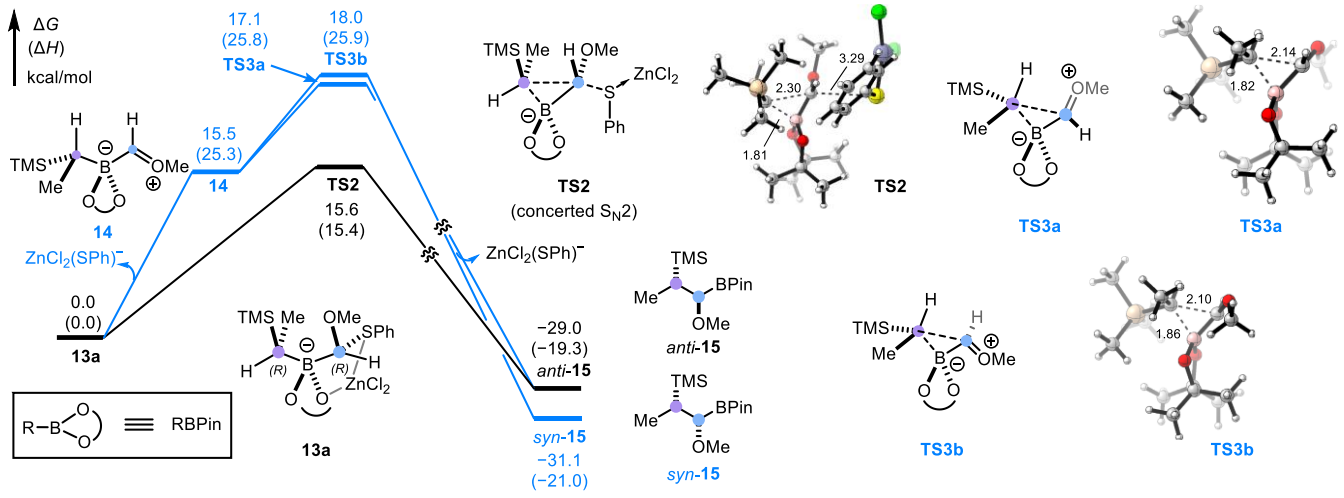
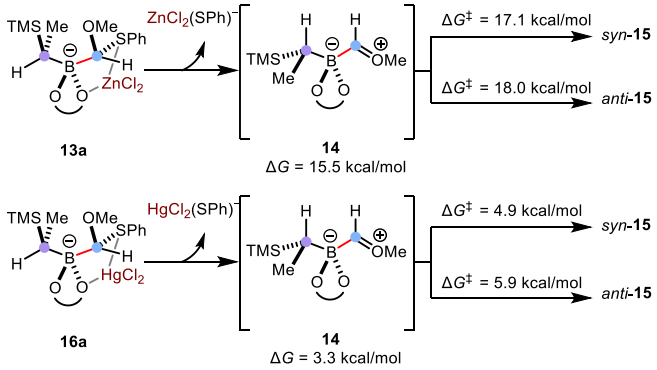


Figure 2. Computed energy profiles of the competing S_N1- and S_N2-type pathways in the $ZnCl_2$-mediated 1,2-migration of boronate complex **13a**. All the boronates used were pinacol boronic esters. DFT calculations were performed at the M06/6-311+G(d,p)/SDD(Zn)/SMD(THF)//B3LYP-D3(BJ)/6-31G(d)/SDD(Zn)/SMD(THF) level of theory. Conformational sampling was performed with CREST at the GFN-xTB2 level of theory.

Scheme 3. $ZnCl_2$/$HgCl_2$-Mediated S_N1-Type 1,2-Migration Pathways[a]



[a]All the boronates used were pinacol boronic esters. DFT calculations were performed at the M06/6-311+G(d,p)/SDD(Zn,Hg)/SMD(THF)//B3LYP-D3(BJ)/6-31G(d)/SDD(Zn,Hg)/SMD(THF) level of theory. Conformational sampling was performed with CREST at the GFN-xTB2 level of theory.

LG dissociation step is endergonic by 15.5 kcal/mol. Because the stereospecific S_N2-type 1,2-migration (**TS2**) leads to complete stereoinversion at the alkoxy-substituted carbon center, this process converts **13a** to the *anti*-diastereomer of the α-methoxy, β-silyl boronate **15**. Upon stereospecific Peterson elimination, an *E*-alkene would be selectively formed, which is consistent with the experimentally observed stereoselectivity when $ZnCl_2$ is used as the Lewis acid. Considering that mercury has stronger thiolate binding affinity than zinc,[19] we surmised that the non-stereospecific S_N1-type 1,2-migration pathway can be more favorable when $HgCl_2$ is used as the Lewis acid. Indeed, the $HgCl_2$-promoted arylthiolate dissociation (from **16a**) is only endergonic by 3.3 kcal/mol, which is 12.2 kcal/mol lower in energy than the analogous $ZnCl_2$-mediated LG dissociation process (Scheme 3). Because intermediate **14** undergoes facile 1,2-migration via **TS3a** and **TS3b** ($\Delta G^{\ddagger}$ = 1.6 and 2.5 kcal/mol with respect to **14**, respectively), the stepwise S_N1-type pathways are much more favorable when the more thiophilic $HgCl_2$ Lewis acid is used, leading to a diminished diastereoselectivity of the homologation product (see entry 3, Table 1).

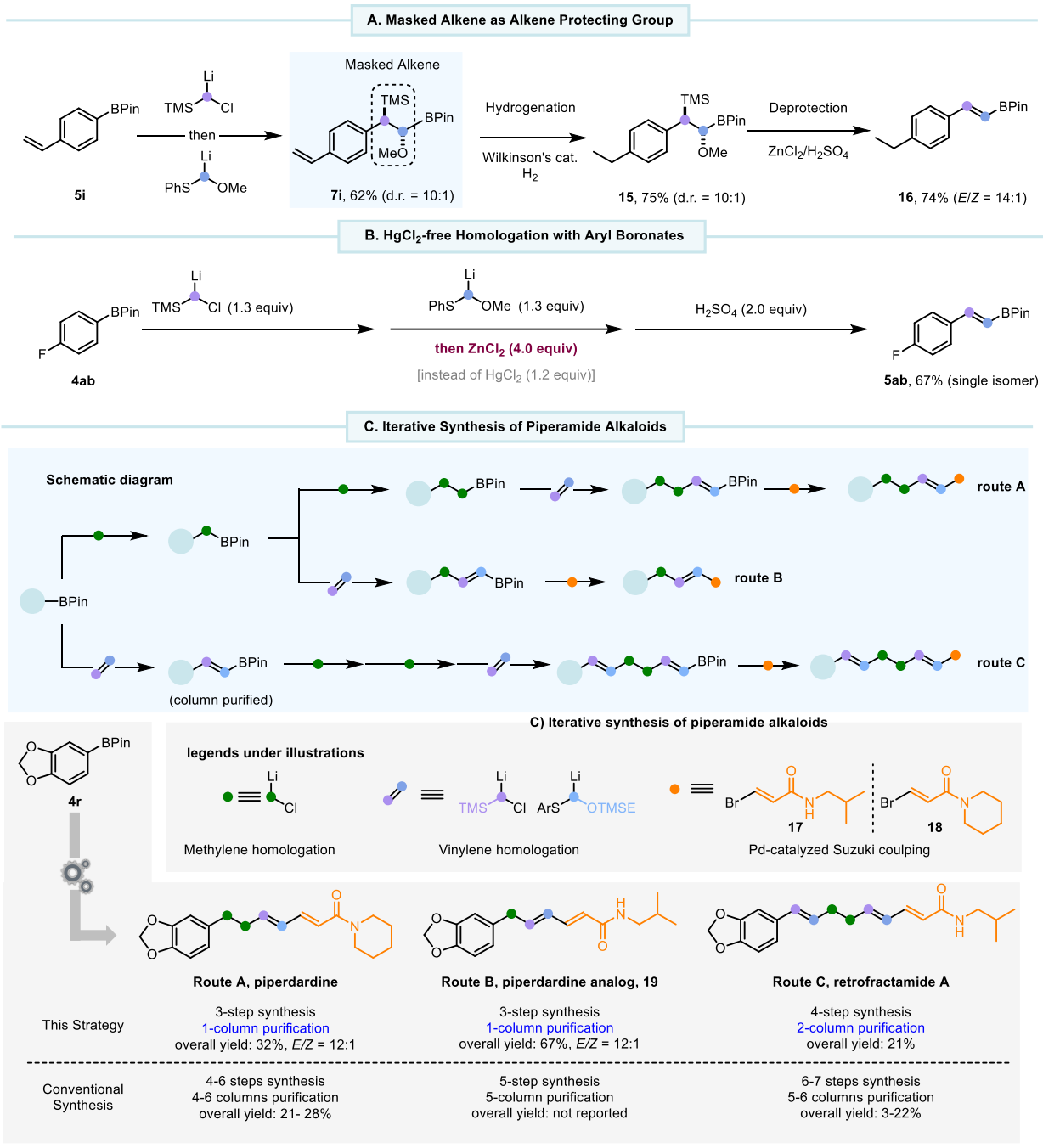
Next, the synthetic utility of the vinylene homologation method has been explored. First, due to the versatile reactivity of alkenylboronates, the homologation product can undergo various facile transformations to access synthetically valuable structural motifs (for details, see Supporting Information, Scheme S1). Additionally, this method can be used to generate a masked alkene moiety, which can survive under hydrogenation conditions (Scheme 4A). Moreover, besides the reactions with alkyl boronates, mercury salts can also be avoided for the homologation with aryl boronates when using 4.0 equivalent of $ZnCl_2$ instead (Scheme 4B).[20] The synthetic potential of this method was further demonstrated in the streamlined syntheses of piperamide-family natural products (Scheme 4C), which have been known to exhibit insecticidal, anti-cancer, and other biological activities.[21] We envisioned that, through merging the vinylene homologation and methylene homologation, the polyene backbone of piperamides could be efficiently accessed by a unified iterative approach. Starting from the common substrate, aryl boronic ester **4r**, piperdardine was efficiently synthesized via a sequence of one-pot double methylene homologation, vinylene homologation, and Suzuki termination with vinyl bromide **18** (**route A**).[22] This three-step synthesis only needs one chromatography with 32% overall yield and 12:1 *E*/*Z* selectivity. The piperdardine analog[23] was prepared in 67% overall yield in a similar manner via **route B**, involving mono methylene homologation, vinylene homologation, and Suzuki termination with vinyl bromide **17**. To access the tri-ene natural product retrofractamide A,[24] the synthesis started with vinylene homologation, next double methylene insertion, and then another vinylene homologation before termination by the Suzuki reaction (**route C**). Compared to the prior approaches to access these compounds, this iterative synthesis strategy uses fewer steps, gives higher overall yield, minimizes purification of reaction intermediates, and more importantly provides programmability to the synthetic design.

Scheme 4. Synthetic Applications

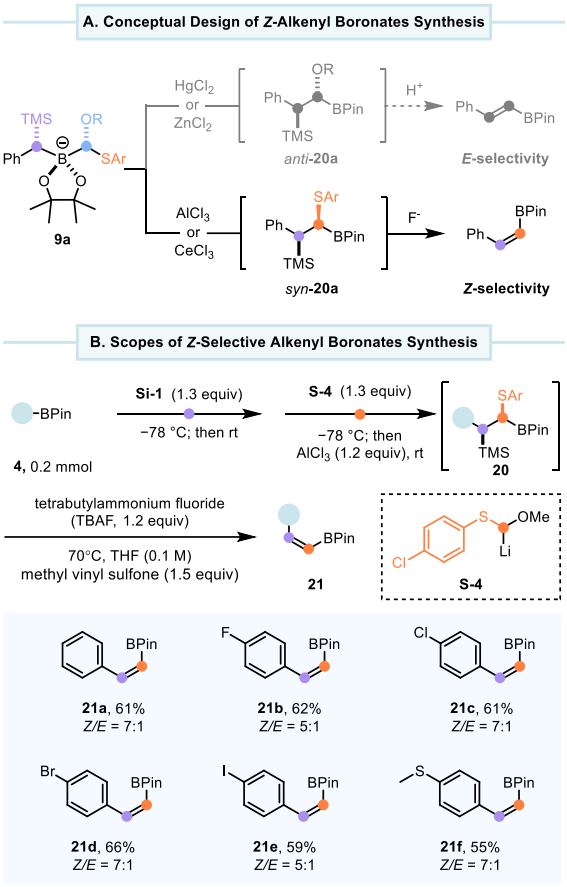
Finally, preliminary success has been obtained with the *Z*-selective vinylene homologation of aryl boronates (Scheme 5). Based on the mechanistic understanding, it is clear that formation of the ate complex (e.g., **9a**) is diastereoselective and soft Lewis acids, such as zinc and mercuric salts, promote arylthiolates as the LG during the 1,2-metallate migration. We therefore postulated that, replacing soft Lewis acids with an oxyphilic (i.e., "hard") Lewis acid, the *syn*-oriented α-thiophenoxy, β-silyl boronate *syn*-**20a** could be selectively obtained by having the alkoxy group as the LG instead (Scheme 5A). To our delight, the LG selectivity in the 1,2-migration step can be altered simply by changing the Lewis acids to $AlCl_3$ or $CeCl_3$. The α-thiophenoxy, β-silyl boronate intermediate **20a** was obtained in high diastereoselectivity (>15:1). Notably, intermediate **20a** exhibited increased stability compared to α-methoxy boronate **7a**, allowing for chromatography purification and spectroscopic characterization. To promote efficient *anti*-elimination, the arylthiolate (**S-4**) containing a para chloro group was found to be a better LG (Scheme 5B). Treatment of intermediates **20** with 1.2 equivalent of TBAF and 1.5 equivalent of methyl vinyl sulfone (to sequestrate the arylthiolate LG that can potentially epimerize **20** through 1,2-metallate migration) afforded the desired Z-alkenylboronates **21a-f** in good yields and synthetically useful diastereoselectivity (for detailed optimizations, see Supporting Information, Table S5).[25] Efforts on improving the *Z* selectivity and expanding to alkyl boronates are ongoing.

CONCLUSIONS

In summary, we have developed the stereoselective vinylene homologation of organoboronates enabled by sequential diastereoselective carbenoid insertion and the Peterson-type elimination. This strategy provides rapid access to various alkenyl boronates from readily available alkyl or aryl boronates, which paves the way for programmable iterative synthesis of complex alkene-containing molecules. The mechanistic insights gained on the diastereoselective carbenoid addition, the Lewis acid-depended 1,2-migration, and divergent reactivity of lithiated alkoxy aryl sulfanes could be valuable to understand the stereochemistry outcomes of similar reactions and have broad implications beyond this work.


A. Masked Alkene as Alkene Protecting Group
Masked Alkene
BPin
TMS
Cl
Li
then
PhS
OMe
5i
7i, 62% (d.r. = 10:1)
Hydrogenation
Wilkinson's cat.
H2
15, 75% (d.r. = 10:1)
Deprotection
ZnCl2/H2SO4
16, 74% (E/Z = 14:1)
B. HgCl2-free Homologation with Aryl Boronates
F
4ab
TMS
Cl (1.3 equiv)
PhS
OMe (1.3 equiv)
then ZnCl2 (4.0 equiv)
[instead of HgCl2 (1.2 equiv)]
H2SO4 (2.0 equiv)
5ab, 67% (single isomer)
C. Iterative Synthesis of Piperamide Alkaloids
Schematic diagram
route A
route B
route C
(column purified)
C) Iterative synthesis of piperamide alkaloids
4r
legends under illustrations
Methylene homologation
Vinylene homologation
ArS
OTMSE
Br
17
18
Pd-catalyzed Suzuki coulping
Route A, piperdardine
Route B, piperdardine analog, 19
Route C, retrofractamide A
This Strategy
3-step synthesis
1-column purification
overall yield: 32%, E/Z = 12:1
3-step synthesis
1-column purification
overall yield: 67%, E/Z = 12:1
4-step synthesis
2-column purification
overall yield: 21%
Conventional Synthesis
4-6 steps synthesis
4-6 columns purification
overall yield: 21- 28%
5-step synthesis
5-column purification
overall yield: not reported
6-7 steps synthesis
5-6 columns purification
overall yield: 3-22%

Scheme 5. *Z*-Vinylene Homologation of Aryl Boronates[a]



[a]All reactions were run on 0.2 mmol, unless noted otherwise. Isolated yields are the overall yields of all operations starting from RBpin.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."
Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

Accession Codes

CCDC 2260049 contains the supplementary crystallographic data for this paper. This 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, U.K.; fax: +44 1223 336033.

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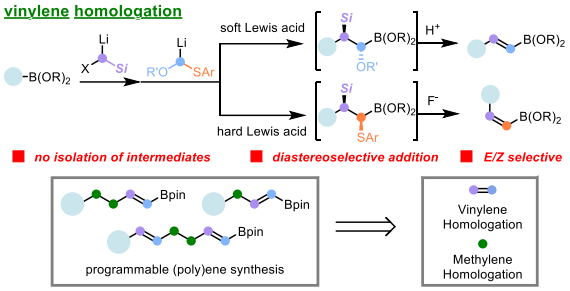
vinylene homologation
soft Lewis acid
hard Lewis acid
no isolation of intermediates
diastereoselective addition
E/Z selective
programmable (poly)ene synthesis
Vinylene Homologation
Methylene Homologation