OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Diborylalkyllithium Salts Trigger Regioselective Ring Opening of Vinyl Aziridines

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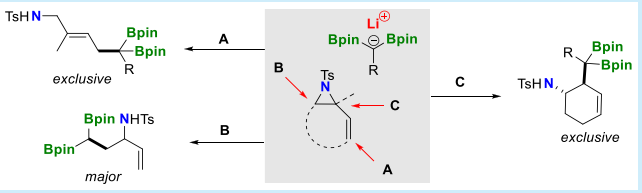
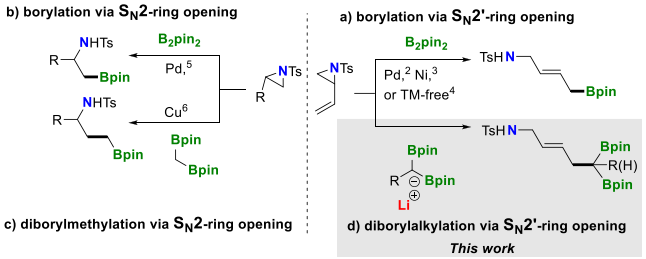
Supporting Information

ABSTRACT: *gem*-Diborylalkanes treated with LiTMP produce α-diborylalkane lithium bases that perform nucleophilic attack on vinyl aziridines with controlled regioselectivity. Preferred S_N2 diborylalkylation ring opening reaction on the less sterically hindered position is observed with 1-tosyl-2-vinylaziridine, whereas exclusive S_N2' nucleophilic attack occurs on 2-methyl-1-tosyl-2-vinylaziridine. Cyclic vinyl aziridines interact through a third venue, via S_N2 diborylalkylation ring opening reaction on the allylic position. Homoallylic diboronates are formed with complete stereochemical control.



Nucleophilic ring opening reactions involving the construction of useful organoboron molecular structures combine the selective control of the ring cleavage together with total atom economy parameters.[1] Versatile allylic amines are efficiently formed from Pd,[2] Ni,[3] or transition metal-free[4] catalyzed borylative S_N2' ring opening of vinyl aziridines with bis(pinacolato)diboron (B_2pin_2), along the concomitant formation of the allylic boronate functionality (Scheme 1a).

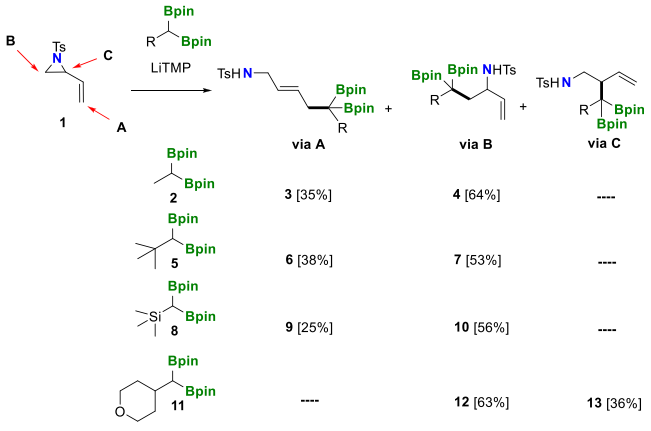
Scheme 1. C−B and C−C Bond Formation through Ring Opening of Alkyl-, Aryl-, and Vinyl Aziridines



Alternatively, S_N2 borylative ring opening reaction of aryl aziridines through a palladium-catalyzed protocol allows the formation of difunctional β-aminoboronate compounds (Scheme 1b).[5] The use of *gem*-diborylmethane instead of B_2pin_2 resulted in the formation of γ-aminoboronic esters through copper-catalyzed ring opening/C−C bond formation of alkyl aziridines in the presence of LiO^{t}Bu (Scheme 1c).[6] However, to the best of our knowledge, the activation of *gem*-diborylalkanes with lithium bases to promote diborylalkylation ring opening of vinyl aziridines is unknown (Scheme 1d), despite the fact that the analogue reaction with epoxides[7] and vinyl epoxides[8] has recently been explored. The activation of *gem*-diborylalkanes with LiTMP via deprotonation and carbanion stabilization allows that both boryl moieties remain in the final product.[9]

To study the viability of our work hypothesis we selected 1-tosyl-2-vinylaziridine (**1**) as model substrate, to react with HC(CH$_3$)(Bpin)$_2$ (**2**) in the presence of 1.2 equiv of LiTMP. When the reaction took place initially at 0 °C (10 min), followed by 16 h at rt, the substrate was quantitatively transformed into two products. The major product was **4** (isolated yield 64%) formed via S_N2 diborylalkylation ring opening reaction on the less sterically hindered position (Scheme 2). However, the S_N2' ring opening reaction became competitive forming the *E*-homoallylboronate product **3** (Scheme 2). Similar reaction outcome was observed using the *gem*-diborylalkanes HC(^{t}Bu)(Bpin)$_2$ (**5**) and HC(Si-

Scheme 2. Diborylalkylation/Ring Opening Reaction of 1-Tosyl-2-vinylaziridine (1)



Received: October 17, 2019

DOI: 10.1021/acs.orglett.9b03672
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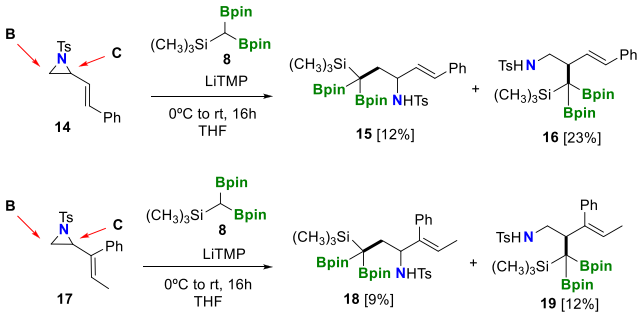
$(CH_3)_3)(Bpin)_2$ (**8**) being the S_N2 ring opening/C−C coupling throughout the less sterically hindered position, the most favored reactivity (Scheme 2).

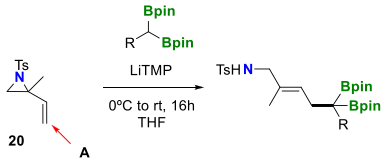
Interestingly, when (tetrahydro-2*H*-pyran-4-yl)methylene-bispinacolboronate (**11**) was employed as the *gem*-diborylalkane reagent, the S_N2' ring opening reaction was weakened, and only products formed via S_N2 pathway were isolated (63% due to the nucleophilic attack on the less sterically hindered position and 36% on the most congested position, Scheme 2). A similar trend was detected when (*E*)-2-styryl-1-tosylaziridine (**14**) was treated with $HC(Si(CH_3)_3)(Bpin)_2$ (**8**) since S_N2' ring opening reaction was suppressed in favor of the nucleophilic attack on the more congested position (Scheme 3). The analogue vinyl aziridine (*E*)-2-(1-phenylprop-1-en-1-yl)-1-tosylaziridine (**17**) also performed a favored diborylalkylation ring opening reaction through S_N2 ring opening, despite the fact that isolated yields on the products diminished significantly, probably due to the instability of the electronically conjugated allylic products (Scheme 3).

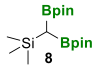
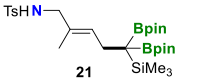
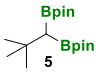
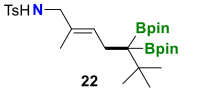
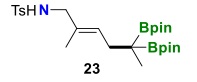
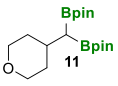
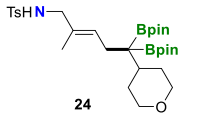
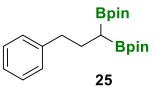
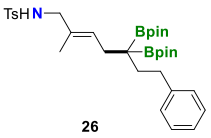
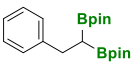
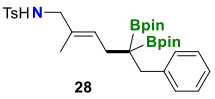
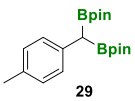
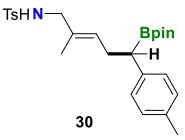
Scheme 3. Diborylalkylation/Ring Opening Reaction of Substituted Vinyl Aziridines 14 and 17



To our delight, when 2-methyl-1-tosyl-2-vinylaziridine (**20**) was explored for diborylalkylation ring opening reaction with reagent $HC(Si(CH_3)_3)(Bpin)_2$ (**8**) and LiTMP, we observed the exclusive formation of the allylic amine/homoallylic boronate **21** as a result of the regioselective nucleophilic attack via S_N2' mechanism (Table 1, entry 1). To the best of our knowledge, this is the first example of a lithium stabilized α-diboryl carbanion reacting along conjugate addition since it has only been reported that diborylmethide lithium salts transmetallate with zinc(II) halide to form the corresponding diborylmethyl zinc(II) species that interact with π-allyliridium intermediates to promote a S_N2 allylic substitution.[10] On the contrary, S_N2' allylic substitution of primary and secondary allylic chlorides with diborylmethane has been reported to proceed in the presence of Cu/NHC catalyst and LiO^tBu (3 equiv), where the NHC ligand (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene]) played an important role in the conjugated mechanism.[11] Even with substoichiometric amounts of base (Cs_2CO_3, 0.5 equiv) in combination with MeOH as solvent and Cu(I) as catalyst without any ligand, the deborylative allyl−alkyl coupling between diborylmethane and vinyl cyclic carbonates has been reported, throughout copper-catalyzed S_N2' ring opening pathway with extrusion of CO_2.[12] Diborylmethane can be also activated with Ag(I) to further transmetalation to π-allylpalladium intermediates in order to conduct the corresponding allyl−alkyl coupling, with the aid of an oxidant to regenerate the Pd(II) species.[13] All these Cu- and Pd- methods have in common that

Table 1. Regioselective S_N2' Diborylalkylation/Ring Opening of 2-Methyl-1-tosyl-2-vinylaziridine (20)[a]



Entry	Diboryl alkane	Product	Isolated Yield [%]
1	 8	 21	[93%]
2	 5	 22	[96%]
3	 2	 23	[98%]
4	 11	 24	[99%]
5	 25	 26	[50%]
6	 27	 28	[75%]
7	 29	 30	[65%]

[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), *gem*-diborylalkanes (0.5 mmol, 1 equiv), LiTMP (0.6 mmol, 1.2 equiv), THF (3 mL), rt, 16 h.

homoallylboronates are selectively formed through allylic reactions while deborylation is undertaken, and consequently, the final product contains only one boryl unit. Here, we report an exclusive S_N2' ring opening of vinylaziridines through diborylalkyllithium salts keeping the two boryl moieties unaltered in the final product. The reaction occurs with complete stereocontrol toward the formation of the (*E*)-isomer as it can be seen in Table 1. This fact was proved doing a NOE experiment of product **21** (see Supporting Information).

When the *gem*-diborylalkanes involved in the reaction were **2**, **5**, or **11**, containing primary, secondary, and tertiary C_β substituents, the isolated yields on the desired product were quantitative (Table 1, entries 2−4). However, the *gem*-diborylalkanes **25** and **27**, containing 1-phenyl-ethyl and benzyl substituents, respectively, proceed toward the ring

DOI: 10.1021/acs.orglett.9b03672
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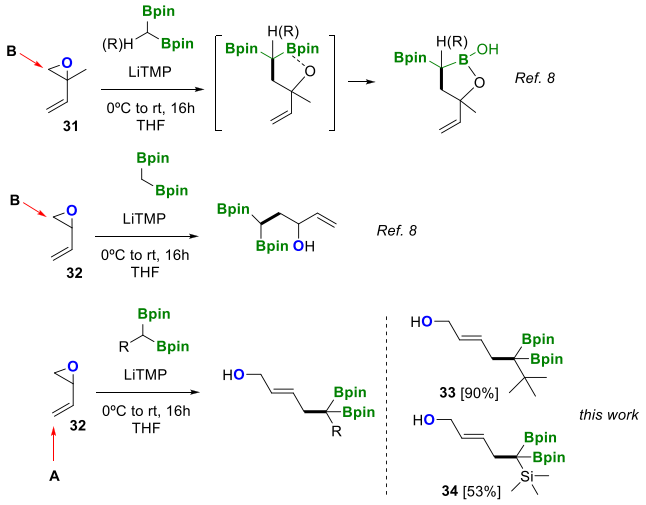
opening C−C cross coupling in moderate isolated yield (Table 1, entries 5−6). No other byproducts were observed, and the lack of the product's stability during the purification process justifies the moderate values of isolated yields. Interestingly, the reaction with HC(*p*-MeC$_6$H$_4$)(Bpin)$_2$ (**29**) allowed the reaction to take place efficiently, although protodeboronation occurred toward the formation of product **30** containing only one boryl moiety (Table 1, entry 7). We suggest that the inner reactivity of the benzylic boron group in the α-diborylbenzyl carbanion might justify the favored protodeboronation under basic conditions.[14]

Remarkably, the observed regioselective diborylmethylation of vinyl aziridine **1** and **20** is significantly different to the one observed in the analogue vinyl epoxides **31** and **32**, under the same reaction conditions (Scheme 4). Nucleophilic attack of

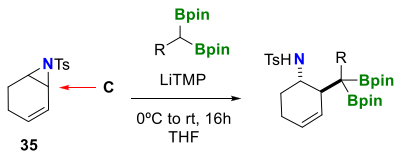
Scheme 4. Diborylalkylation Ring Opening Reaction of Substituted Vinyl Epoxides 31 and 32

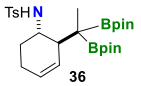
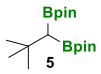
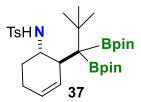
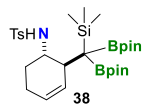
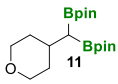
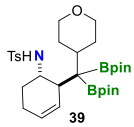
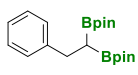
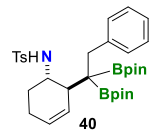
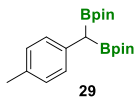
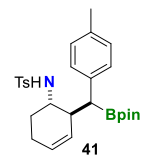


diborylalkyllithium salts occurred exclusively at the homoallylic position of **31**, with concomitant intramolecular cyclization to give the substituted 3-borylated 1,2-oxaborolan-2-ol product (Scheme 4).[8] The substrate 2-vinyloxirane (**32**) also provides the S$_N$2 ring opening with H$_2$CB$_2$pin$_2$,[8] whereas the use of substituted diboryllkyllithium salts favors the exclusive S$_N$2′ ring opening/C−C coupling as we demonstrated in this work (Scheme 4).

Next, we explored the diborylalkylation/ring opening of cyclic vinyl aziridines such as 7-tosyl-7-azabicyclo[4.1.0]hept-2-ene (**35**),[15] and in contrast to the observed S$_N$2′ ring opening of noncyclic vinylaziridine **20**, we found that **35** suffered a S$_N$2 nucleophilic attack at the allylic position, instead (Table 2). The reaction is stereocontrolled forming exclusively homoallyldiboronate species with *trans* disposition of the NHTs and CR(Bpin)$_2$ groups, keeping the two boryl moieties unaltered in the final product. With substituted *gem*-diborylalkanes **2**, **5**, **8**, and **11**, containing primary, secondary, and tertiary C$_\beta$ substituents, the regioselective S$_N$2 ring opening was efficiently performed isolating quantitative percentages of the desired homoallyldiboronate products **36**−**39** (Table 2, entries 1−4). Reagent **27** containing the benzyl group also allowed the formation of the desired homoallyldiboronate species **40** in moderate isolated yield (Table 2, entry 5). However, when the phenyl substituted *gem*-diborylalkane **29** is involved in the reaction, we observed that

Table 2. Regioselective S$_N$2 Diborylalkylation/Ring Opening of 7-Tosyl-7-azabicyclo[4.1.0]hept-2-ene (35)[a]



Entry	Diboryl alkane	Product	Isolated Yield [%]
1	 2	 36	[98%]
2	 5	 37	[98%]
3	 8	 38	[99%]
4	 11	 39	[96%]
5	 27	 40	[51%]
6	 29	 41	[66%]

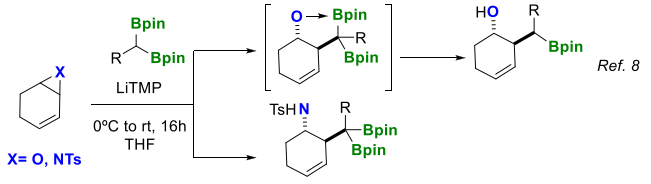
[a]Reaction conditions: substrate (0.4 mmol, 0.8 equiv), *gem*-diborylalkanes (0.5 mmol, 1 equiv), LiTMP (0.6 mmol, 1.2 equiv), THF (3 mL), rt, 16h.

the coupled product **41** retained only one boryl moiety, suggesting the protodeboronation pathway as a consequence of the α-diborylbenzyl carbanion's reactivity (Table 2, entry 6). Both entries 5 and 6 provided quantitative conversion on the desired products without any observation of byproduct formation, although isolated yields were moderate due to the instability of products during purification.

A similar protodeboronation sequence was involved in the diborylalkylation of the analogue cyclic vinyl epoxide 3,4-epoxy-1-cyclohexene (**42**), providing the homoallylboronate products with only one boryl moiety at the final product, independently of R = aryl or alkyl group (Scheme 5).[6] It suggests that the OH functionality might favor the intramolecular deborylation in a sterically hindered quaternary C

DOI: 10.1021/acs.orglett.9b03672
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 5. Comparative Diborylalkylation Ring-Opening Reaction of Cyclic Vinyl Epoxide and Vinyl Aziridine



center,[16] whereas in the case of the amine group this interaction might not be favored.

It can be concluded that α-diboryl carbanions formed from *gem*-diborylalkanes and LiTMP perform regioselective nucleophilic attack on vinyl aziridines. Preferred S_N2 ring opening/C−C bond forming on the less sterically hindered 1-tosyl-2-vinylaziridine in contrast to the favored S_N2' diborylalkylation on 2-methyl-1-tosyl-2-vinylaziridine. In contrast to the two previous examples, the allylic position of cyclic vinyl aziridines traps the α-diboryl carbanions along the diborylalkylation/ring opening to form exclusively homoallyldiboronate species with *trans* disposition of the amine and diborylalkyl groups. Despite the fact that regioselectivity depends on the nature of vinyl aziridine substrate, the resulting product maintains the two boryl moieties unaltered, except for those reactions where $HCArB_2pin_2$ are involved since protodeboronation seems to proceed, under the basic reaction conditions, in order to diminish the steric hindrance around the quaternary C centers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03672.

Experimental Procedures and spectra data, as well as ^1H, ^{13}C, and ^{11}B spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Spanish Ministerio de Ciencia, Innovación y Universidades (MCIU) through project FEDER-CTQ2016-80328-P.

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(3) Crotti, S.; Bertolini, F.; Macchia, S.; Pineschi, M. *Org. Lett.* **2009**, *11*, 3762.
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DOI: 10.1021/acs.orglett.9b03672
Org. Lett. XXXX, XXX, XXX−XXX