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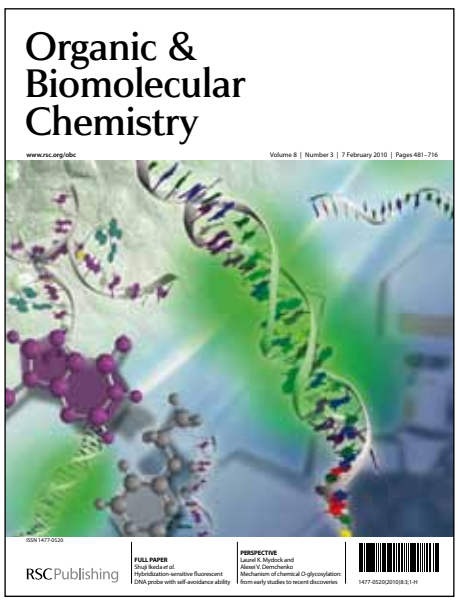

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Metal-Free Borylative Ring-Opening of Vinyl Epoxides and Aziridines

Xavier Sanz,[a,b] Graham M. Lee,[a,c] Cristina Pubill-Ulldemolins,*[a,b] Amadeu Bonet,[a] Henrik Gulyás,[a] Stephen A. Westcott,[c] Carles Bo,*[b] Elena Fernández*[a]

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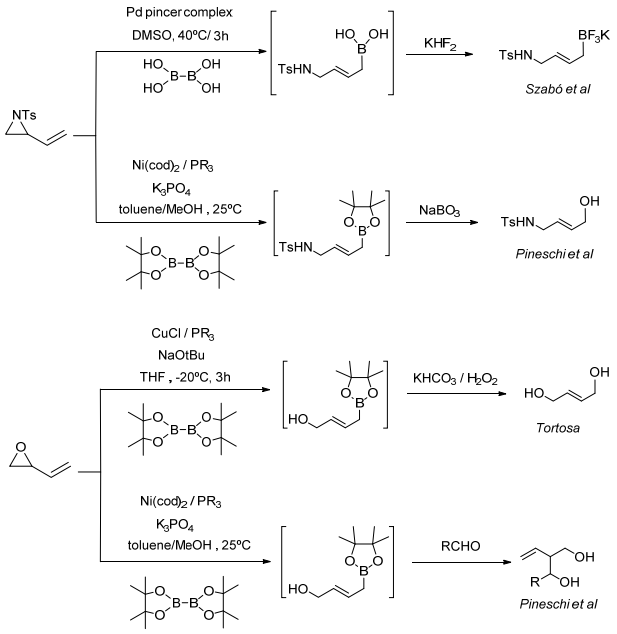
A rational approach towards the borylative ring-opening of vinyl- epoxides and vinylaziridines, by the *in situ* formed MeO^-→bis(pinacolato) diboron adduct, has been developed. The enhanced nucleophilic character of Bpin (sp^2) moiety from the reagent favours the S_N2' conjugated B addition with the concomitant aperture of the epoxide and aziridine rings. The reaction proceeds with total chemoselectivity towards the polyfunctionalised (-OH, or -NHTs) allyl boronate. Theoretical calculations have determined the transition states that come from the reaction of the vinylic substrates with the activated MeO^-→bis(pinacolato)diboron adduct, and a plausible mechanism for the organocatalytic borylative ring opening reaction has been suggested.

Introduction

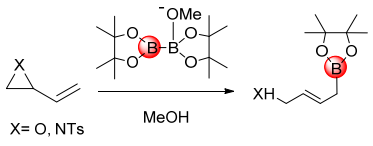
The activation of tetraalkoxydiboron reagents, to selectively transfer the boryl moiety to unsaturated substrates, has always been associated with the cleavage of the B-B bond by transition metal complexes. But outstanding advances in the field have emerged from the simple activation of $(RO)_2B\text{-}B(OR)_2$ via Lewis acid-base interactions, achieving an organocatalytic chemo-, regio- and enantioselective control on the C-B bond formation.[1] During the last few years, selective metal-free β-boration[2] and diboration[3] of activated and unactivated alkenes, respectively, have illustrated the potential of this new methodology, but still many other applications of boron addition reactions remain unexplored. It is known that the borylative ring opening of vinylcyclopropanes,[4,5] vinyl- epoxides[6,7] and vinylaziridines,[4,6] has exclusively been studied by activation of pinB-Bpin or $(HO)_2B\text{-}B(OH)_2$ with Pd, Ni and Cu complexes (Scheme 1). In these transformations the mechanism has not been well established but certain features indicate that the activation of the diboron reagent could take place via σ-bond metathesis. This assumption is mostly supported by the fact that base is required[8] to guarantee the efficiency of the ring opening allylic borylation.

Results and discussion

Based on our previously developed protocols, [2b,c,f] we decided to launch a study on the catalytic synthesis of allyl boronates, excluding the application of transition metals, aiming at establishing a convenient organocatalytic methodology. Specifically, we focused our efforts to study the transfer of a nucleophilic boryl unit,[9] from an *in situ* formed MeO^-→bis(pinacolato)diboron adduct,[2c,10] to vinyl epoxides and vinyl aziridines (Scheme 2).

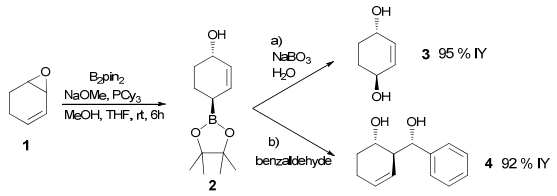


Scheme 1. Metal mediated borylative ring-opening of vinyl epoxides and aziridines

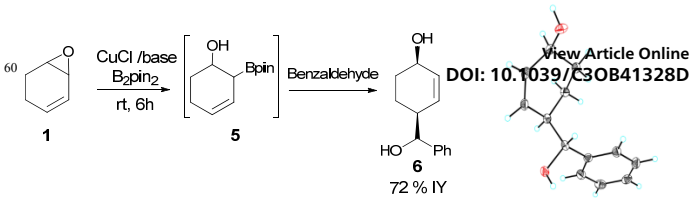


Scheme 2. Metal-free approach towards borylative ring-opening of vinyl epoxides and aziridines

Considering 3,4-epoxy-1-cyclohexene (**1**) as a model substrate, the nucleophilic pinacolboryl unit can attack three electron deficient reactive sites, that is the C_3 and C_4 carbons of the epoxide ring and the C_1 carbon of the C=C double bond. We have experimentally observed (Scheme 3) that following mixing **1** and the *in situ* generated MeO^-→bis(pinacolato)diboron adduct in the presence of 10 mol% of PCy_3, the nucleophilic pinacolboryl unit exclusively attacked at the double bond providing the 1,4-cyclohexenyl hydroxyboronate (**2**) via a S_N2' pathway, within 6h at room temperature (Table 1, entry 1). NaOMe was determined to be the most efficient base to assist the *in situ* MeO^-→bis(pinacolato)diboron adduct formation. The organoborane **2** could be isolated and fully characterized. One single diastereomer was formed in the reaction which was identified as the trans isomer by (i) oxidizing the C-B bond with $NaBO_3$ (Scheme 3a) and (ii) reacting **2** with benzaldehyde (Scheme 3b). The stereostructures of the corresponding 1,4-diol (**3**) and 1,3-diol (**4**) were determined by ^1H NMR spectroscopy. When the organocatalytic borylative ring-opening of **1** was carried out in the absence of PCy_3, only moderate conversion was observed (55%, 6h). The essential contribution of basic phosphines to enhance the nucleophilic B addition has already been studied.[11] Interestingly, in a comparative study carried out using CuCl to activate the B_2pin_2 we found that the transition metal catalyzed reaction afforded the 1,2-cyclohexenyl hydroxyboronate (**5**) via S_N2 addition (Scheme 4). That is, the presence of Cu(I) and base, favoured the formation of Cu-Bpin,[1,9] and the nucleophilic Bpin moeity attacked the epoxy group, while the C=C double bond remained intact (Table 1, entry 2). In this particular case, the product **5** could not be isolated and therefore its stereoselectivity was not determined, but its reaction with benzaldehyde provided the *cis*-4-hydroxy-cyclohex-2-enyl-phenyl-methanol (**6**). The X-Ray structure of **6** confirmed the *cis* arrangement of the 1,4-subtituents on the disubstituted cyclohexene (Scheme 4). The different reactivity observed between the copper mediated borylation and the metal-free approach could be understood by the relative increase in nucleophilic character of the Bpin moiety when attached to Cu than when bonded to the sp^3 Bpin counterpart.[9d] However, the unexpected finding about the stereoselectivity on compound **5** is still under study.

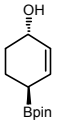
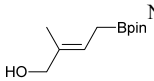
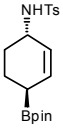


Scheme 3. Organocatalytic borylative ring-opening of **1** and reactivity of the allylboronate **2** with $NaBO_3$ and benzaldehyde



Scheme 4. Copper mediated chemoselective nucleophilic Bpin attack on the epoxide functional group of 3,4-epoxy-1-cyclohexene (**1**). X-Ray structure of 4-hydroxy-cyclohex-2-enyl-phenyl-methanol (**6**)

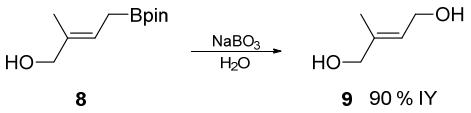
Table 1. Organocatalytic borylative ring-opening of vinyl epoxides and vinyl aziridines with B_2pin_2.

Entry	Substrate	Product	Base (mmol)	T (ºC)	t (h)	Conv. (%)	Isolated Yield (%)
1[a]	 1	 2	NaOMe (0.06)	25	6	99	62
			NaOMe (0.03)	25	6	72	
			NaOtBu (0.03)	25	6	71	
			Cs_2CO_3 (0.03)	25	6	20	
2[b]	 1	 5	Cs_2CO_3 (0.06)	25	6	88	72[c]
3[a]	 7	 8	NaOMe (0.06)	50	20	99	66
4[a]	 10	 13	NaOMe (0.06)	50	20	90	68

[a] Standard conditions: substrate (0.3 mmol), diboron reagent: B_2pin_2 = bis(pinacolato)diboron, (0.45 mmol), PCy_3 (0.03 mmol), MeOH (2.5 mmol), THF (3 mL). [b] substrate (0.3 mmol), diboron reagent: B_2pin_2 (0.45 mmol), CuCl (0.015 mmol), MeOH (2.5 mmol), THF (3 mL). [c] Isolated as 4-hydroxy-cyclohex-2-enyl-phenyl-methanol (**6**).

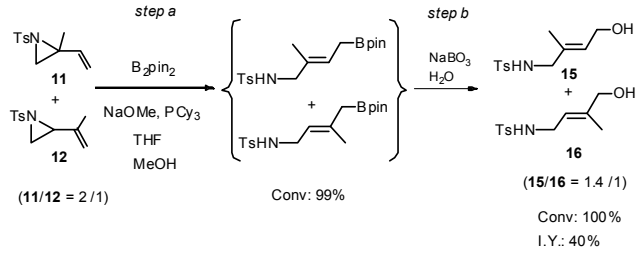
To survey the scope of the organocatalytic borylative ring-opening methodology, we next studied the reaction between the adduct MeO^-→bis(pinacolato)diboron and 2-methyl-2-vinyloxirane (**7**). We found that, as in the case of the cyclic epoxide **1**, the C-B bond was formed via a bimolecular allylic substitution (Table 1, entry 3). The relative position of the functional groups was established by oxidation of 2-methyl-4-pinacolboryl-butenol (**8**) to the corresponding 2-methyl-1,4-

butendiol (**9**) (Scheme 5). By comparison with reported ^{1}H NMR data for the E isomer of **9**,[12] we determined that **8,** was formed as the *E* isomer.



Scheme 5. Oxidation of the allylboronate **8** with $NaBO_3$

Acyclic and cyclic 2-vinyl aziridines have been synthetized in this work in order to compare the influence of the different heteroatoms in the borylative ring-opening via S_N2' pathway. Following the methodolody established in the literature,[13] we prepared the 3,4-aziridine-1-cyclohexene (**10**), 2-methyl-2-vinylaziridine (**11**) and 3-methyl-2-vinylaziridine (**12**), via the Evans-type direct monoaziridination of cyclohexadiene and 2-methyl butadiene using [*N*-(*p*-toluenesulfonyl) imino]iodinane (PhI=NTs) and $Cu(acac)_2$. When the adduct MeO^-→bis(pinacolato)diboron reacted with **10**, exclusive formation of 1,4-cyclohexenyl tosylaminoboronate (**13**) was observed (Table 1, entry 4). The isolation of compound **13** and comparison with reported NMR data for this polyfunctionalised compound,[6] allowed to be characterized as the *trans* isomer. In agreement with the organocatalytic borylative ring opening reaction of **1**, these reactions are stereoselective for the *trans* isomer, although in the case of the cyclic aziridine longer reaction time and a slight increase in temperature were required for complete conversion (Table 1, entry 4). Oxidation of **13** towards 1,4-cyclohexenyl tosylaminoalcohol (**14**) confirmed the trans isomer formation. The substrates 2-methyl-2-vinylaziridine (**11**) and 3-methyl-2-vinylaziridine (**12**), were prepared as a 2:1 mixture and the borylative ring opening reaction proceeded with total conversion towards a mixture of amino functionalized allyl boronate compouds, which could be isolated via oxidation as a mixture of 2-methyl-1-tosylamino-4-butenol and 3-methyl-1-tosylamino-4-butenol (1:0.7)[6] (Scheme 6). The prevalence of the borylative ring-opening via S_N2' pathway has also been demonstrated in these acyclic vinyl aziridines. It has to be said that by product formation was not observed and the isolated yields of the products were only moderate due to the instability of the functionalized allylic boronate compounds.



Scheme 6. Borylative ring opening of **11** and **12**, followed by in situ oxidation. Step a: Substrate (0.3 mmol), diboron reagent: B_2pin_2 (bis(pinacolato)diboron), (0.45 mmol), NaOMe (0.6 mmol), PCy_3 (0.03 mmol), MeOH (2.5 mmol), THF (3 mL), r.t., 6h.

In order to get deeper insight into the mechanism of the organocatalytic borylative ring-opening of vinyl epoxides and aziridines, we carried out a DFT based study on the main intermediates and transition state. As our group has previously shown,[2c,f],[3] the crucial additives for activating B_2pin_2 are Brönsted base and MeOH to generate MeO^-→bis(pinacolato)diboron adduct. Also in the present case, this adduct is key starting point in the general mechanism for the base/alcohol borylative ring-opening of epoxides and aziridines as depicted in Figure 1, which shows the elementary steps of the reaction between B_2pin_2 and 3,4-epoxy-1-cyclohexene (**1**) as a model substrate. First, the methoxide ion, generated from MeOH in the presence of base, forms a Lewis acid-base adduct with the diboron reagent, the MeO^-→bis(pinacolato)diboron adduct, which we chose as the origin of energies. In the next step, a transition state (**TS1**) was fully characterized and described as an S_N2' reaction that involves a nucleophilic attack of the adduct sp^2 boron moiety at the $\mathbf{C_1}$ carbon atom of the double bond, in a concerted manner with the concomitant opening of the epoxide ring. This interaction was identified as the overlap between the strongly polarized B-B σ bond (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the vinyl epoxide (Figure 2).

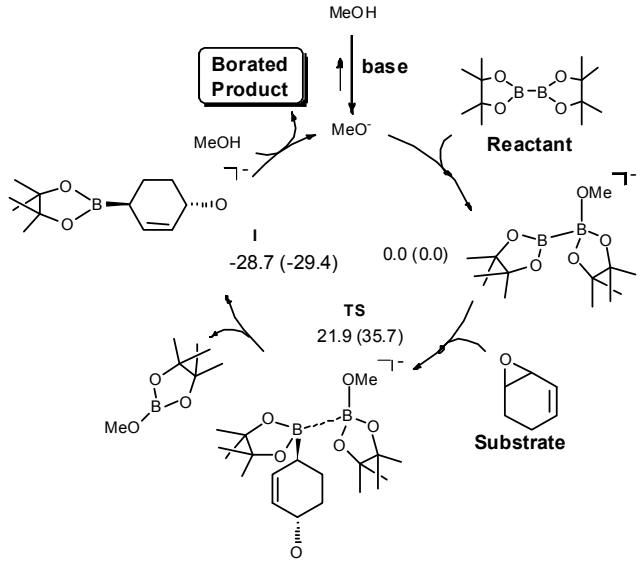


Figure 1. Proposed reaction pathway for the borylative ring-opening of vinyl epoxides and vinyl aziridines with B_2pin_2. Electronic energy and Gibbs free energy (in parenthesis) computed at the BP86 level relative to $B_2pin_2 \cdot MeO^-$ adduct plus 3,4-epoxy-1-cyclohexene as a model substrate. All values in kcal·mol^{-1}

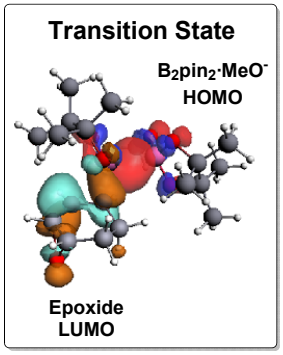


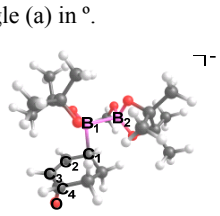
Figure 2. An illustration of TS1 frontier orbitals HOMO (red-blue) and LUMO (orange-cyan) for **1**.

The structural features of the **TS1** clearly reflect the cleavage of the B-B bond (from 1.701 in free B_2pin_2, to 1.755 in $B_2pin_2{\cdot}MeO^-$, to 2.096 in **TS1** (Å)), and the formation of the new B-C_1 bond (1.988 Å). Also, according to the C-C bond distances, an allylic type rearrangement can be observed, the C_1-C_2 bond distance increases (from 1.344 in the substrate to 1.417 in **TS1**) while the C_2-C_3 bond distance decreases (from 1.483 in the substrate to 1.438 in **TS1**), suggesting the formation of the new C_2=C_3 double bond. Importantly, the C_3-C_4-O angle increases only slightly from the substrate to the transition state (60.6 and 67.9 respectively). Although this is indicative of concomitant aperture of the epoxide ring, regarding this parameters the transition state is rather early. Remarkably, the enhancement of electron density in the oxygen atom (Voronoi charge in the substrate -0.24 to -0.36 in the TS) corroborates that charge redistribution has taken place. The **TS1** structure releases the "(pin)BOMe" byproduct and directly leads to formation of an anionic intermediate **I** in which the epoxide ring is completely open (C_3-C_4-O angle 110.6, Voronoi charge in the oxygen atom -0.74). Further protonation of this **I** species in the presence of the excess of MeOH provide the desired allyl boronate product, and in this way methoxide ions are regenerated.

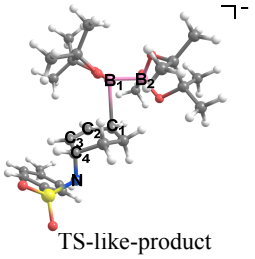
The configuration of the final allylboronate product was exclusively characterized as the *trans* isomer since the nucleopilic attack of the sp^2 boron moiety to C_1 occurs in *anti* with regard to the epoxide functional group. In addition to considering the different conformations of this **TS1** and possible stereoisomers of the substrate (See SI for more details), we did also evaluate the attack in *syn* that would lead to the *cis* product. However, the TS1-*syn* was found to be more energetically demanding ($\Delta\Delta E$=+5.8; $\Delta\Delta G$=+4.3 kcal.mol^{-1}) than TS1-*anti* (see SI for more details). These computational findings are in well agreement with the experimental data, since with all the studied substrates, the *trans* allylboronate product was the only one formed. Note that both transition sates, **TS1** and TS1-*syn* were located and characterized for the other substrates (1, 7, 10, 11 and 12, see SI), being the *syn* attack the more energetically demanding in all the cases. Although the nucleophilic attack in *anti* is the energetically favoured for all the considered substrates, we did found notable structural differences between the **TS1** for vinyl epoxides and the analogous tosyl aziridines. Considering the bond distances of the new C_2=C_3 bonds as well as the bond angles C_3-C_4-O/N in the **TS1** (Table 2, entry 1 and 2), it is clear that the structures of the **TS1** in the case of the epoxides resemble more the features of reactants in free form than the intermediate **I**. Contrarily, the structural features of **TS1** for aziridines are closer to those of the intermediates **I**, that is the C_2=C_3 bond distances are shorter than in the case of epoxides and the C_3-C_4-N bond angles are larger (Table 2, entries 3, 4 and 5). Epoxides have an early **TS1** while tosyl aziridines have a late **TS1**. This can be understood taking into account that the developed charge on the nitrogen due to the charge redistribution upon the nucleophilic attack is stabilized by the tosyl group.

This stabilizating effect of the tosyl group is also reflected in the energy values of the **TS1**, there is a clear trend: the TS's for aziridines are less energetically demanding than for epoxides (Table 3, entries A, B, C, D and E. Note that both $\Delta E^{\neq}$ and $\Delta G^{\neq}$ values are aprox. 9-10 kcal.mol^{-1} lower for aziridines than for epoxides). Thus, tosyl aziridines seem to be more reactive than epoxides to undergo the S_N2' borylative ring-opening process.

Table 2. Molecular structures for TS1 with the vinyl epoxides and aziridines. Selected bond distances (d) are given in Å and bond angle (a) in º.



TS-like-reactants



TS-like-product

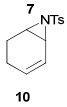
Entry	Substrate	d(C_2-C_3)	d(C_3-O)	α (C_3-C_4-O/N)	
				TS1	**I**
1		1.438	1.624	67.9	110.6
2		1.418	1.865	80.9	112.1
3		1.399	2.118	91.1	113.7
4		1.410	2.207	96.0	112.1
5		1.410	2.102	90.5	110.4

Table 3. Relative electronic energy (kcal.mol^{-1}) and Gibbs energy (kcal.mol^{-1}) for the activation of the studied vinyl epoxides and aziridines[a].

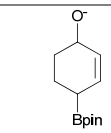
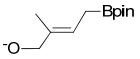
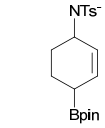
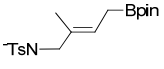
Entry	Entry in Table 1	Substrate	$\Delta E^{\neq}$	ΔEr	$\Delta G^{\neq}$	ΔGr
A	1	 **1**	21.9 (20.4)	-28.7 (-30.8)	35.7 (34.2)	-29.4 (-31.4)
B	2	 **7**	17.3 (16.1)	-30.3 (-30.7)	31.0 (29.8)	-31.5 (-31.9)
C	3	 **10**	11.2 (11.6)	-56.5 (-61.0)	26.7 (27.1)	-54.4 (-58.9)
D	4	 **11**	8.9 (10.8)	-59.4 (-59.6)	25.3 (27.1)	-56.2 (-56.4)
E	5	 **12**	10.2 (14.3)	-64.2 (-64.5)	27.0 (31.0)	-61.7 (-62.0)

[a] Molecular geometries for all the species were optimized using BP86 as a functional. Single point energies at the metahybrid M06 level are in parenthesis. Additional calculations in the Supporting Information.

Also, the resulting anionic **I** species with tosyl aziridines are thermodynamically more stable than the corresponding epoxides derived (Table 3, entries A, B, C, D and E, ΔE_r and ΔG_r values, difference of aprox. 30 kcal.mol^{-1}). Remarkably, independently of the DFT functional used or considering dispersion effects with the M06 functional, or even including solvent effects (see SI) the general trend remains equal: vinyl tosylaziridines seem more reactive, and their products are more stable, than the corresponding epoxides. Comparing the studied vinyl epoxides, the energy barrier for the **TS1** of the acyclic 2-methyl-2-vinyloxirane (**7**) is lower than for the cyclic (**1**) (Table 3, entry A respect to B, $\Delta\Delta E$=-4.1; $\Delta\Delta G$=-4.7 kcal.mol^{-1} lower). Aziridines follow the same trend (Table 3, entry C respect to D, $\Delta\Delta E$=-2.3; $\Delta\Delta G$=-1.4 kcal.mol^{-1} lower), being lesser energetically demanding than epoxides. This result can be rationalized by the fact that terminal double bonds are more reactive than internal ones. Note the high stability of the aziridines derived intermediates, in which the negative charge is stabilised by the tosyl group.

We also calculated the pKa values for the anionic intermediate species, and values are collected in Table 4. As expected, vinyl-alkoxides are more basic that the corresponding vinyl-amidures. At the same level of theory, we evaluated[11] the pKa of the strong Verkade's base (23.4), value that almost matched the experimental value (26.8). Values in Table 4 suggest that both vinyl-amidures and vinyl-alkoxides are as basic, or even more, than Verkade's base, so also able to deprotonate methanol.

Table 4. Computed pKa values for the intermediate species.

Entry	**I**	pKa
1		35.6
2		34.5
3		22.3
4		23.6

For all the studied substrates, we also determined the energy barrier for the nucleophilic attack of the MeO$^-$→bis(pinacolato)diboron adduct to the epoxide and aziridine group, this is at C_3 instead of at C_1. In all the cases, the attack that would give rise to unobserved products present higher energy barriers than mechanism delineated above (See SI). Thus, the presented computational results also corroborate the prevalence of the borylative ring-opening via S_N2' in absence of Cu catalyst.

Conclusions

We have developed a metal-free borylative ring opening of vinyl epoxides and vinyl aziridines. The sole addition of B_2pin_2 with a base and MeOH provided *in situ* the MeO$^-$→bis(pinacolato)diboron adduct. As a consequence of this Lewis acid-base interaction, the sp^2 Bpin moiety acquired an enhanced nucleophilic character that allowed the attack at the conjugated C=C of epoxides or aziridines, throughout a S_N2' pathway. Further functionalization of the allylboronate products via oxidation or reactivity with benzaldehyde allowed to confirm the stereostructures. From a theoretical point of view, we proposed a plausible mechanism for the metal-free borylation of cyclic and non-cyclic vinyl epoxides and aziridines. The mechanism is in accordance with our experimental results and helps to understand the role of each reagent in the reaction

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Experimental Section

General procedures for the Organocatalytic Borylative Ring-Opening of Vinyl Epoxides and Vinyl Aziridines with B_2pin_2.

Borylation of 3,4-epoxy-1-cyclohexene (1). *Organocatalytic method:* The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and bis(pinacolato)diboron (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate (33 µL, 0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at room temperature for 6 hours. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR showing that one single product was formed from the substrate. The obtained 4-cyclohexenyl hydroxyboronate (**2**) was purified by flash chromatography using a silica gel column previously deactivated with triethylamine, and a mixture of petroleum ether and ethyl acetate (10:3) as eluent (R.f.=0.35). The product could be isolated in 41.7 mg (62% yield).

Borylation of 2-methyl-2-vinyloxirane (7): The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and bis(pinacolato)diboron (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate (33 µL, 0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at 50ºC for 20 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to probe that one single product was formed from the substrate. The obtained 2-methyl-4-pinacolboryl-butenol (**8**) was purified by flash chromatography using a silica gel column previously treated with triethylamine, and a mixture of petroleum ether and ethyl acetate (1:1) as eluent (R.f.=0.42). The product could be isolated in 42.0 mg (66% yield).

Borylation of 3,4-aziridine-1-cyclohexene (10): The phosphine PCy_3 (9.54 mg, 10 mol%), sodium methoxide (33.4 mg, 0.6 mmol) and bis(pinacolato)diboron (114 mg, 0.45mmol) were transferred into an oven-dried Schlenk tube under argon. THF (3 mL) was added. The mixture was stirred for 10 minutes at room temperature to dissolve the phosphine and the borane reagent completely. The substrate (0.3 mmol) and MeOH (100 µl, 2.5 mmol) were added, and the reaction mixture was stirred at 50ºC for 20 hours. The reaction mixture was cooled to room temperature. An aliquot of 0.2 mL was taken from the solution and gently concentrated on a rotary evaporator at RT, and analyzed by ^{1}H-NMR to probe that one single product was formed from the substrate. The obtained 1,4-cyclohexenyl tosylaminoboronate (**13**) was purified by flash chromatography using a silica gel column previously traeted with triethylamine, and a mixture of petroleum ether and ethyl acetate (7:3) as eluent (R.f.=0.49). The product could be isolated in 80.3 mg (71% yield).

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The oxidation protocol: The allyl boronates obtained in the above described procedure were converted into the corresponding alcohols in the following manner. To the crude organoboron product (cc. 0.3 mmol) in THF (3 mL), sodium perborate (90 mg, 0.9 mmol) and water (3 mL) were added. The reaction mixture was stirred vigorously overnight at room temperature. The reaction mixture was diluted with water and then extracted with dichloromethane (3 x 20mL). The combined organic phase was dried over $MgSO_4$ and concentrated. Product **3** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.70). The product could be isolated in 32.5 mg (95% yield). Product **9** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.75). The product could be isolated in 27.6 mg (90% yield).

4.Allylation reaction of allyl boronates with benzaldehyde: The allyl boronates **2** and **5** obtained in the organocatalytic and copper mediated borylation, respectively, were derivatized with benzaldehyde. To the crude organoboron product (cc. 0.3 mmol) in THF (3 mL), benzaldehyde (100 µL, 0.9 mmol) was added. The reaction mixture was stirred vigorously overnight at room temperature. Product **4** was purified by flash chromatography using a silica gel column with ethyl acetate as eluent (R.f.=0.80). The product could be isolated in 56.4 mg (92% yield). Product **6** was purified by flash chromatography using a silica gel column and a a mixture of petroleum ether and ethyl acetate (7:3) as eluent (R.f.=0.49). The product could be isolated in 38.6 mg (63% yield).

DFT studies: Molecular structures for all species were optimized without constraints using DFT-based methods as implemented in the Amsterdam Density Functional (ADF v2009.01) package.[14,15] A triple-ξ plus polarization Slater basis set was used on all atoms. Relativistic corrections were introduced by scalar-relativistic zero-order regular approximation (ZORA).[16] For geometry optimizations we used the local VWN correlation potential[17] together with the Becke exchange and the Perdew correlation[18-20] (BP86) generalized gradient (GGA) corrections. Stationary points in the potential energy hypersurface were characterized either as minima or transition states by means of harmonic vibrational frequency calculations. Solvent effects were introduced by using the continuous solvent model COSMO.[21] Single-point energy evaluations at the metahybrid M06[22] level were performed self-consistently.

Notes and references

[a] *Department de Química Física i Inorgànica*
Univ. Rovira i Virgili, C/ Marcel.lí Domingo s/n, 43007 Tarragona (Spain)
Fax: (+) 34 977 559563
E-mail: mariaelena.fernandez@urv.cat ,
http://www.quimica.urv.cat/tecat/catalytic_organoborane_chemistry.php
[b] *Institute of Chemical Research of Catalonia (ICIQ). Avda. Països Catalans, 17. 43007 Tarragona (Spain)*
[c] *Department of Chemistry and Biochemistry, Mount Allison University, Canada*

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