Very Important Publication

Synthesis of Allylboronates via Zweifel-type Deprotonative Olefination

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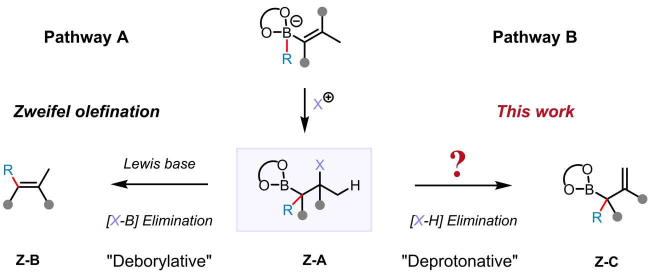
Abstract: A method for the synthesis of allylboronates via Zweifel-type deprotonative olefination was demonstrated. Tetrasubstituted vinylboronates were used as the substrates. NCS (*N*-chlorosuccinimide) was used as a bifunctional additive, electrophile and base. This method exhibited a different elimination strategy in Zweifel type transformation to afford allylboronates. The homo-alcohols and alkenes were stereoselective synthesized from the obtained allylboronates, demonstrating the synthetic value of this methodology.

Keywords: Boron; Zweifel Olefination; Allylic Compounds; Vinylboronates

As one of the boron-related name reactions, the Zweifel olefination has been recognized as a powerful method for the deborylative synthesis of stereospecific alkenes.[1] Generally in Zweifel olefination, tetracoordinated vinylboronates were initially formed, followed by a halo-electrophile induced 1,2-metalate rearrangement.[1c] As a result, the β-halo alkylboron compound **Z-A** was generated as the intermediate. Then, a Lewis base promoted halo-boron [X–B] elimination achieves the deborylative olefination to give the product **Z-B** (Scheme 1, Pathway A). Overall, the C–B bond is replaced by C–C bond. This process has been a mindset under Zweifel olefination conditions over the past decades.[1c] Theoretically, according to the structure of **Z-A**, the halo-proton [X–H] elimination might also be possible when it contains β-H at another side of the C–X moiety of **Z-A**. In this case, the deprotonation allows the reservation of the C–B bond in the product to synthesize allylboronates **Z-C** (Scheme 1, Pathway B). The highly valuable allylboronates in organic synthesis including name reaction Antilla allylboraton have attracted tremendous efforts on their synthesis.[2] The realization of this hypothesis by deprotonation but not conventional deborylation under Zweifel olefination conditions may provide a new alternative choice. However, this potential route has not been disclosed during the past decades of Zweifel olefinations.[1c] Herein, we demon-

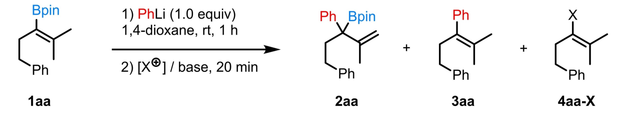


Scheme 1. The Conventional Zweifel Olefination and a New Deprotonative Hypothesis (this work)

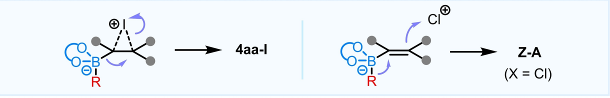
strate this unprecedented route to synthesize various allylboronates (Scheme 1, Pathway B).

Generally, Iodine is used as the halo-electrophile in Zweifel olefination. NaOH or NaOMe is usually used as the base. These Lewis bases are easy to coordinate to the boron-center. As a result, halo-boron elimination occurs to give the Zweifel olefination product (Scheme 1, Pathway A). Therefore, to achieve the Pathway B hypothesis in Scheme 1, coordinative Lewis base needs to be avoided and non-coordinative Brønsted base is preferred. Based on these considerations, initial studies were carried out by using a tetra-substituted alkenyl pinacol boronate **1 aa** as the model substrate (Table 1). When the reaction was conducted in the presence of PhLi under the traditional Zweifel olefination condition (I_2/NaOMe/MeOH, Table 1, entry 1), the deborylative olefination product **3 aa** was obtained together with the iodination product **4 aa-I**. The desired allylboronate **2 aa** was not observed. When the reaction was carried out by using I_2 as the halo-electrophile in the absence of NaOMe/MeOH (entry 2), only the iodination product **4 aa-I** was observed. Using NIS instead of I_2 resulted in increased yield of **4 aa-I**. Importantly, the desired **2 aa** was observed in trace amount in this case (entry 3). Obviously, when NIS was used, succinimide anion will be generated as the side product, which can behave as a Brønsted base to promote deprotonation for the generation of **2 aa** (Scheme 1, Pathway B). In the case of iodo-electrophile, it is easy to form zwitterionic iodonium intermediate,[1a] which might be the reason for the generation of iodination product **4 aa-I**. We envisioned that using the bromo- or chloro-electrophiles might reduce the generation of halogenation products, as they might not be easy to form oniums. Especially for chloro-electrophile, it might occur a synergetic electrophilic chlorination and 1,2-migration to generate **Z-A** (Table 1).[3] Indeed, when NBS was used instead of NIS, the bromination product **4 aa-Br** was not detected. Meanwhile, the yield of desired allylboronate **2 aa** was increased to 54% with the observation of **3 aa** in trace amount (entry 4). When NCS was used, the yield of **2 aa** increased to 63% with the detection of **3 aa** and the chlorination product **4 aa-Cl** in trace amounts (entry 5), demonstrating that NCS provided the best chemoselectivity for the synthesis of allylboronate. Since a small amount of substrate **1 aa** remained by using 1.0 equivalent of NCS, we tried to increase the amount of NCS to 1.6 equivalents to give the optimal result and **2 aa** was obtained in 73% yield (entry 6, see the screening of NCS equivalent in SI). Only trace amount of **3 aa** and **4 aa-Cl** were observed in this case.

Table 1. Reaction parameters

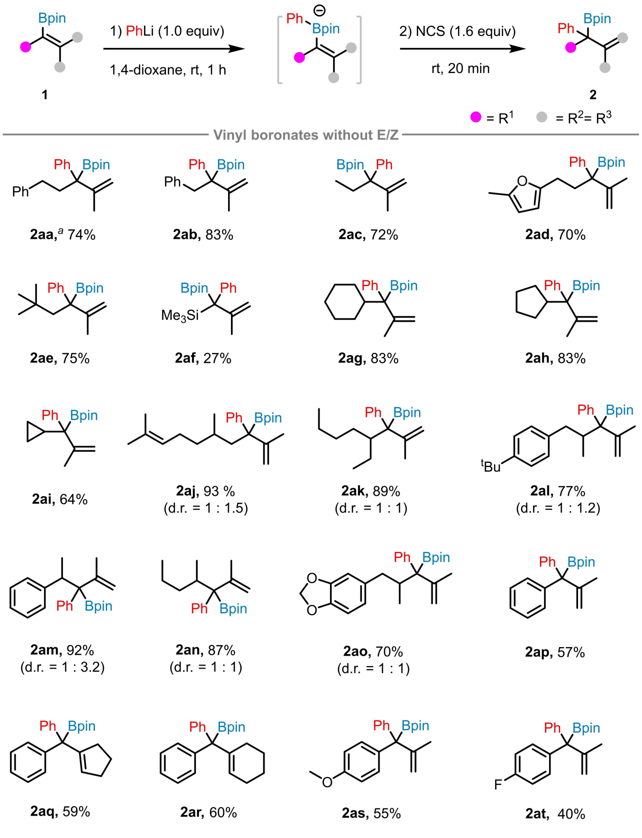


Entry	[X⊕] / base (1.0 equiv)	**2aa**[b]	**3aa**[b]	**4aa-X**[b]
1	I_2/NaOMe/MeOH	nd	48%	21% (X = I)
2	I_2/--	nd	trace	56% (X = I)
3	NIS/--	trace	trace	90% (X = I)
4	NBS/--	54%	trace	nd (X = Br)
5	NCS/--	63%	trace	trace (X = Cl)
6	**NCS/-- (1.6 equiv)**	**73%**	**trace**	**trace (X = Cl)**



Conditions: **1 aa** (0.2 mmol), PhLi (0.2 mmol), X□ (0.2 mmol), 1,4-dioxane (1.0 mL), rt; [b] Determined by GC analysis using naphthalene as the internal standard.

Next, the substrate scope of deprotonative olefination was explored (Scheme 2). By using phenyllithium reagent as the nucleophile, the transformation pro-



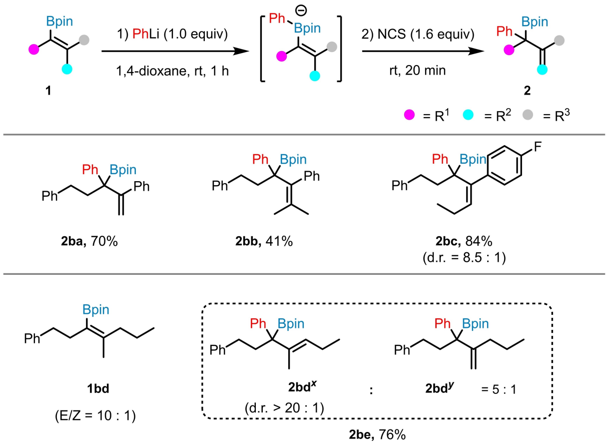
Scheme 2. Conditions: **1** (0.2 mmol), PhLi (1.0 equiv, 0.2 mmol), NCS (1.6 equiv, 0.32 mmol, 0.32 M in 1,4-dioxane), 1,4-dioxane (1.0 mL), rt for 20 min in N_2 atmosphere. Yields are based on isolated products. The *d.r.* value was determined by ^{1}H NMR analysis. [a] A 5.0 mmol scale reaction afforded 1.20 grams of **2 aa** (See details in SI).

ceeded efficiently with various tetra-substituted vinyl boronates, which were prepared by Boron-Wittig reaction,[4] approaching the allyl boronates in high selectivity. With different R^1 group, the relevant allyl boronates were obtained in good yields from 70% to 83% (**2ab**–**2ae**, Scheme 2). In the case of *gem*-silylboryl alkene, the allyl silylboronate was produced in 27% yield (**2af**), in which a low selectivity between deprotonative process and deborylative process was observed. No desired product was observed and only Zweifel olefination product was obtained in 62% yield in the case of 1,1-diborylalkene (**1da** in SI). In regard to the cycloalkyl substituted vinylboronates under the standard condition, the corresponding allyl boronates were obtained in good yields (**2ag**–**2ai**). Notably, the vinylboronates bearing β-substituent proceeded well to give the desired products, while low diastereoselectivity was observed (**2ak**–**2ao**). To our delight, the vinylboronates bearing a C=C double bond was compatible to afford allylboronate under the reaction condition (**2aj**).

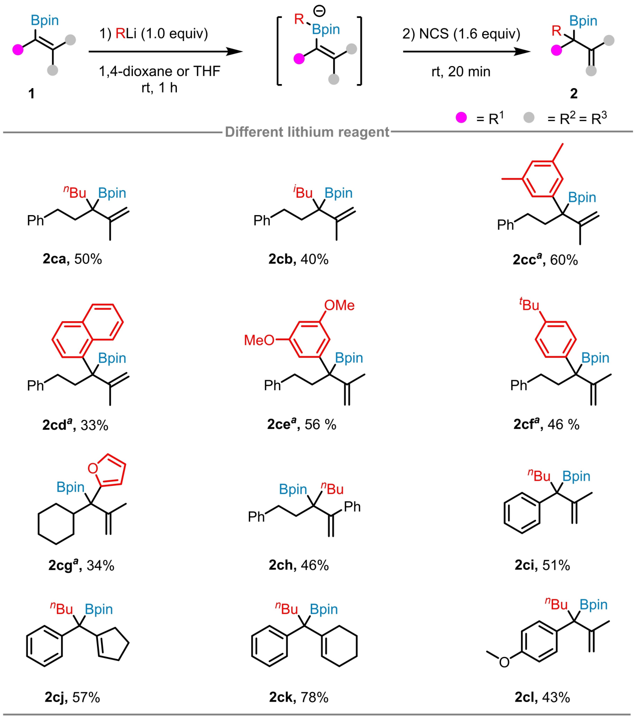
Having done the investigation of the alkyl substituted vinylboronates, we turned our attention to the type of phenyl α-substituted vinyl boronates with the strategy of constructing the tetra-substituted vinylboronates developed by our group.[5] To our delight, under the standard condition, the desired *gem*-diaryl allylboronates were well obtained in moderate yields (Scheme 2, **2ap**–**2at**). A significant amount of their corresponding tetra-substituted alkenes were observed for this type of compounds (See details in SI). Obviously, the tetrasubstituted vinylboronates were typically used in Scheme 2. Those tri- and di-substituted vinylboronates were also tested under the standard condition, the deborylation products dominated in the reaction mixture.

When R^2 was an alkyl group and R^3 was an aryl group, the reaction also proceeded well to give the desired products (Scheme 3, **2ba**–**2bc**). In the case of **2bc**, the R^2 was a propyl group, the allyl boronate **2bc** was obtained in 84% yield with the observation of E/Z isomers (d.r. = 8.5:1). In the case of two different alkyl groups bearing hydrogens for R^2 and R^3, there might be two possible deprotonations. For example, when R^2 = Me and R^3 = *n*-Pr (**1bd**), two isomeric allylboronates were indeed observed with the internal olefin as the major product (**2bd^x**:**2bd^y** = 5:1). Meanwhile, the internal alkene was obtained in an excellent stereoselectivity of d.r. > 20:1.

Next, the expansion of organolithium reagents was further studied to demonstrate the wide-range scope of application (Scheme 4). The **1aa** was used as standard substrate to explore the applicability of different lithium reagent. When *n*-BuLi and *i*-BuLi were used to replace PhLi, the reactions proceeded well to afford 50% and 40% of the desired products, respectively (**2ca**, **2cb**). The reason for the relatively low yield was the generation of by-product tetrasubstituted olefins via Zweifel olefination pathway. When MeLi was employed as the nucleophile, the product was only



Scheme 3. Stereoselective synthesis of allyl boronates, reaction conditions: **1** (0.2 mmol), PhLi (1.0 equiv, 0.2 mmol), NCS (1.6 equiv, 0.32 mmol, 0.32 M in 1,4-dioxane), 1,4-dioxane (1.0 mL), rt for 20 min in N_2 atmosphere, yields are based on isolated products. The *d.r.* value was determined by GC analysis.

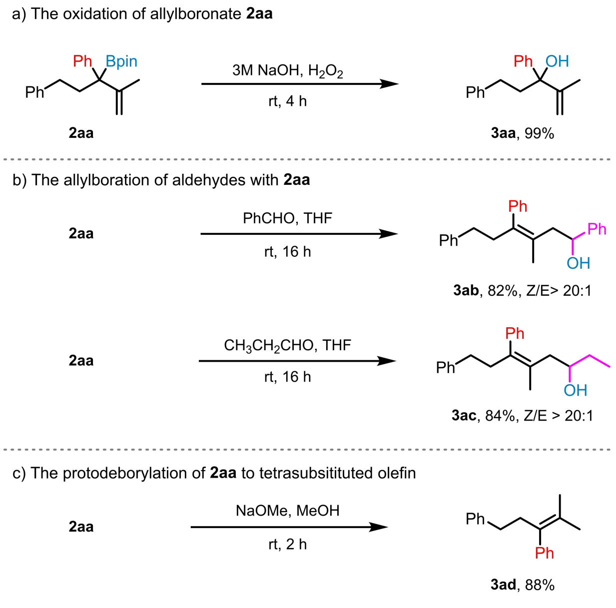


Scheme 4. Conditions: **1** (0.2 mmol), Organolithium reagent (1.0 equiv, 0.2 mmol), 1,4-dioxane (1.0 mL), rt for 1 hour then adding NCS (1.6 equiv, 0.32 mmol, 0.32 M in 1,4-dioxane), rt for 20 min. [a]ArLi (0.25 mmol) was made in-situ (see details in SI), THF (1.0 mL), NCS (1.6 equiv, 0.32 mmol, 0.32 M in 1,4-dioxane). Yields are based on isolated products.

detected in trace amount which might be owing to the poor migratory aptitude and sensitivity towards steric hindrance of methyl group.[6] Then, several *in-situ* prepared ArLi were subjected to react with vinylboronates under the standard conditions. Moderate yields of the desired allylboronates were obtained (**2 cc–2 cf**). When the heterocyclic aromatic furyllithium reagent was used, the allyl boronate was obtained in 34% yield (**2 cg**). With *n*-BuLi as the nucleophile, several vinylboronates were tested, the corresponding products were afforded in moderate to good yields (**2 ch–2 cl**), demonstrating that the butyl group is also a general migrating group in this transformation.

As a highly valuable synthetic building block, allylboronates have been widely used in organic synthesis. Then, several typical transformations of allylboronates were demonstrated by using **2 aa** as the standard substrate (Scheme 5). The oxidation of boryl group was first conducted to access allyl tertiary alcohol **3 aa** in nearly quantitative yield (Scheme 5a). Next, the allylborations of benzaldehyde and propionaldehyde were examined with **2 aa**, which provided the corresponding homoallyl alcohols **3 ab** and **3 ac** in 82% and 84% yield respectively with excellent stereoselectivity (Z/E > 20:1) (Scheme 5b).[7] The protodeborylation of **2 aa** in the presence of NaOMe in MeOH solvent afforded the corresponding tetrasubstituted alkene **3 ad** in 88% yield (Scheme 5c).

In summary, a synthetic method for the synthesis of allyl boronates under Zweifel-type olefination conditions was achieved. Different to the Zweifel olefination, the intermediate, after the electrophile-induced 1,2-metalate rearrangement, underwent selective [X–H] elimination to keep the boryl group in the product, as a result to afford valuable allyl boronates. NCS was used as the electrophilic halogenation reagent. The transformation of allyl boronates was performed to demonstrate the synthetic utility of this method.



Scheme 5. Synthetic applications of allyl boronates

Experimental Section

General Procedure for Transformation of Vinylboronates to Allylboronates: To a 25 mL flame-dried resealable reaction tube of solvent flask equipped with a magnetic stirring bar was added vinylboronates (0.20 mmol), 1.4-dioxane (1.0 mL) under nitrogen atmosphere. Subsequently, PhLi (0.20 mmol, 1.0 M in Et_2O) was added dropwise to the mixture at room temperature, the tube was sealed with Teflon screw cap and the reaction mixture was stirred for 1 hour. Then, under the protection of nitrogen atmosphere, NCS (0.32 mmol, 0.32 M in 1,4-dioxane) was added dropwise to the reaction mixture through a syringe at room temperature and the resulting solution was stirred for another 20 minutes. Upon completion, the reaction was quenched by ethyl acetate and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel and eluted with petroleum ether : ethyl acetate (50:1 to 20:1) to afford the desired allylboronates.

Acknowledgements

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