Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Synthesis of Alkenyl Boronates from Epoxides with Di-[B(pin)]-methane via Pd-Catalyzed Dehydroboration

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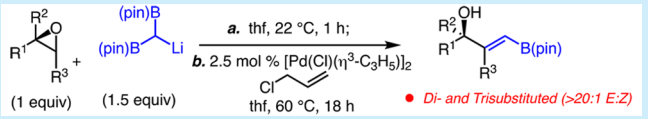
Supporting Information

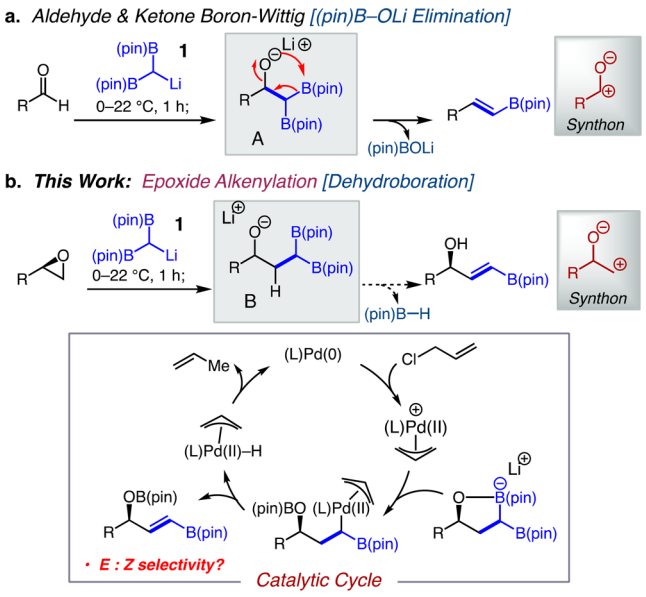
ABSTRACT: A practical and broadly applicable catalytic method for the synthesis of (*E*)-alkenylborons is presented. Reactions are promoted by $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$ and proceed by the dehydroboration of cyclic borates. Through the use of epoxides and readily available di-B(pin)-methane (pin = pinacolato), a range of allylic alcohol-containing alkenyl boronates, including those that contain a tertiary alcohol, may be prepared in up to 75% yield and >20:1 *E*/*Z*.



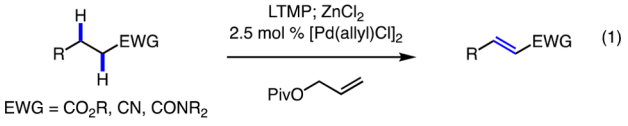
Alkenylboronic acid pinacol esters are versatile molecules for organic synthesis.[1] As such, a variety of methods have been developed for their preparation; these include alkene cross-metathesis,[2,3] alkyne hydroboration,[4] alkyne reduction,[5] cross-coupling,[6] and alkene C−H borylation.[7] Of considerable value are protocols that in tandem efficiently form stereodefined alkenylborons as well as establishing allylic functionality.[8]

In addition to the former methods, the boron-Wittig reaction represents an efficient metal-free process for the stereoselective generation of alkenyl boronates by the coupling of aldehydes or ketones with readily available 1,1-diborylalkanes (Scheme 1).[9] For example, addition of $[(pin)B]_2C(H)Li$ (**1**) to an aldehyde results in 1,2-positioned alkoxide and B(pin) groups (e.g., **A**), which undergo elimination via the loss of (pin)BOLi. In connection to research associated with the development of 1,1-diborons as useful reagents for stereoselective synthesis, we became interested in the use of epoxides as electrophilic coupling partners, which represent charge-separated synthons (vs carbonyls). As a result, the addition of $[(pin)B]_2C(H)Li$ to an epoxide leads to 1,3-disposed alkoxide and B(pin) moieties incapable of eliminating (e.g., **B**) and ready to participate in further reactions.[10] We hypothesized that the loss of H−B(pin) from **B** would provide a simple strategy for the synthesis of alkenyl boronates bearing an allylic alcohol with stereochemistry arising from the chiral epoxide. Such a process could be accomplished by the use of palladium catalysis to effect a formal dehydroboration, via a transmetalation and *β*-hydride elimination sequence of events. Newhouse and co-workers reported a related efficient dehydrogenation strategy that employs a Pd salt and an allyl oxidant for the synthesis of *α*,*β*-unsaturated amides, esters, and nitriles via zinc enolates (eq 1).[11] In this regard, we decided to see if a similar approach could be applied to the dehydroboration of intermediates such as **B** for the preparation of alkenylborons.

Scheme 1. Synthesis of Alkenyl Boronates with Diborylmethane



- *Pd-Catalyzed α-,β-Dehydrogenation (Newhouse)*



Herein, we report the stereoselective alkenylation of epoxides by a coupling/dehydroboration method that simultaneously generates a stereodefined allylic alcohol and (*E*)-alkenyl boronic ester. The overall transformation represents the direct alkenylation of an epoxide, equivalent to a stereoselective aldehyde alkenylation.

We initiated our studies with the coupling of (*R*)-styrene oxide **2** and **1** (Table 1). Subjecting epoxide **2** to $[(pin)B]_2C(H)Li$ in THF at 22 °C for 1 h, followed by treatment with 2.5 mol % of

Received: December 9, 2017

DOI: 10.1021/acs.orglett.7b03853
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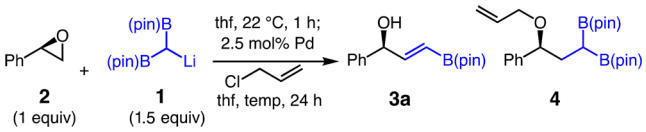
Table 1. Reaction Optimization[a]



entry	Pd catalyst	temp °C	conv (%); 3/4[b]	E/Z[b]
1	$[Pd(allyl)Cl]_2$	20	<5; –	
2	$[Pd(allyl)Cl]_2$	40	42; >98:2	>20:1
3	$[Pd(allyl)Cl]_2$	60	63; >98:2	>20:1
4	$Pd(Ph_3)_4$	60	59; <2:98	
5	$PdCl_2$(dppb)	60	76; <2:98	
6	$PdCl_2$(dppf)	60	46; <2:98	
7	$Pd(dba)_2$, binap	60	63; <2:98	
8[c]	$[Pd(allyl)Cl]_2$	60	62; >98:2	>20:1
9[d]	$[Pd(allyl)Cl]_2$	60	60; >98:2	>20:1

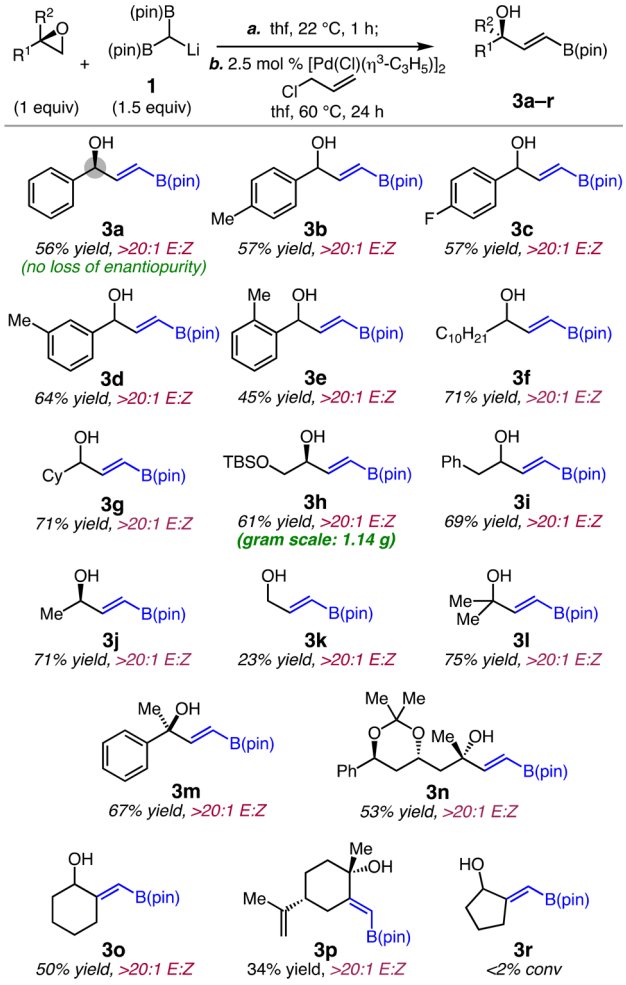
[a]Reactions performed under N_2 atm. [b]Values determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with DMF as internal standard. [c]Reaction run at [0.16 M]. [d]Reaction run at [0.05 M].

$[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$ and allyl chloride as the oxidant, resulted in <5% conversion to desired alkenyl boronate **3** (entry 1). It was found, however, that increasing the temperature to 40 and 60 °C (entries 2 and 3) facilitates the reaction, affording the desired product in 42 and 63% yield, respectively, as the (*E*)-alkene isomer (>20:1).[12] Other palladium sources such as $Pd(PPh_3)_4$ (entry 4), $PdCl_2$(dppb) (entry 5), $PdCl_2$(dppf) (entry 6), and $PdCl_2$(binap) were found to be ineffective and only afforded significant amounts of the *O*-allyl product **4**.

With optimal conditions in hand, we next set out to explore the reaction scope. As illustrated in Scheme 2, the alkenyl boronate synthesis is general for a wide variety of epoxides. Transformations proceed in the presence of 2.5 mol % of $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$ and allyl chloride (3 equiv) in THF at 60 °C for 24 h. Various aryl-substituted epoxides can be effectively converted through the alkenylation process into the corresponding alkenyl boronates (**3a**–**e**) in good yields (45–67% yield) and stereoselectivity (>20:1 *E*/*Z*). Notably, it was found that there is no loss in enantiopurity in the formation of **3a** when (*R*)-styrene oxide (99:1 er) is employed. The transformation is also effective for the preparation of alkyl-substituted alkenyl boronic esters. Under standard conditions, a wide variety of terminal alkyl epoxides, including those that contain methyl, cyclohexyl, phenyl, and TBS-ether functionality, can be converted efficiently and stereoselectively into (*E*)-alkenyl boronic esters **3f**–**3j** in 61–71% isolated yield. It was found that the epoxide alkenylation reaction is amenable to gram-scale preparation of alkenyl boronic esters, as demonstrated by the preparation of 1.14 g of enantioenriched allylic alcohol **3h** under standard conditions. Unsubstituted and volatile ethylene oxide can also be employed in the catalytic dehydroboration process to furnish allylic alcohol **3k** as a single alkene isomer, albeit in diminished 23% yield. Alkenyl boronates derived from 1,1-disubstituted epoxides are formed equally effectively. Such examples include isobutylene oxide and α-methylstyrene oxide derived alkenyl boronates **3l** and **3m** generated in 75 and 67% isolated yield, respectively. Furthermore, the reaction is tolerant of existing stereocenters as tertiary alcohol **3n** is formed in a 53% yield and >20:1 *E*/*Z*.

Internal six-membered 1,2-disubstituted epoxides perform equally well for the stereoselective synthesis of trisubstituted alkenylborons. Under standard conditions in Scheme 2, $[(pin)B]_2C(H)Li$ (**1**) opens the ring of the cyclohexene oxide

Scheme 2. Alkenyl Boron Synthesis Epoxide Scope[a,b]



[a]Reactions performed under N_2 atm. [b]Yield represents isolated yield of purified material and is an average of two experiments.

as well as sterically hindered limonene oxide, and subsequent Pd-catalyzed dehydroboration furnishes **3o** and **3p** in 50 and 34% yield (>20:1 *E*/*Z*). This is in contrast to the reaction with cyclopentene oxide (**3r**), which does not undergo ring opening with carbanion **1**.

The alkenylation process was also found to work well with more complex progesterone- and androsterone-derived 1,1-disubstituted epoxides (Figure 1). For example, following epoxide opening at 45 °C with **1** (1.5 equiv), **4** and **5** are efficiently generated in 47 and 67% yield, respectively. As previously noted in our bis-electrophile couplings with **1**,[10] modification of the 1,1-diboron fragment with additional groups

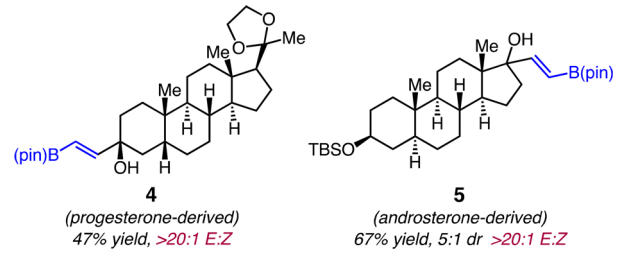


Figure 1. Alkenylation of steroid-derived epoxides.

DOI: 10.1021/acs.orglett.7b03853
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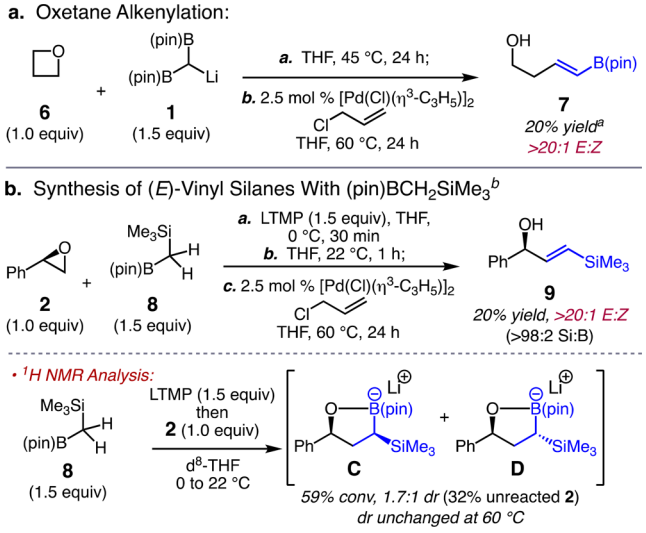
(e.g., $[(pin)B]_2C(H)Me$) is not tolerated in the dehydroboration.

The robustness of the alkenylboron protocol was found to extend to variations in both the cyclic ether and nucleophile components, such as oxetane **6** and borylsilyl methane **8** (Scheme 3). First, it was found that parent oxetane (**6**) can be

Scheme 3. Additional Substrate Variation



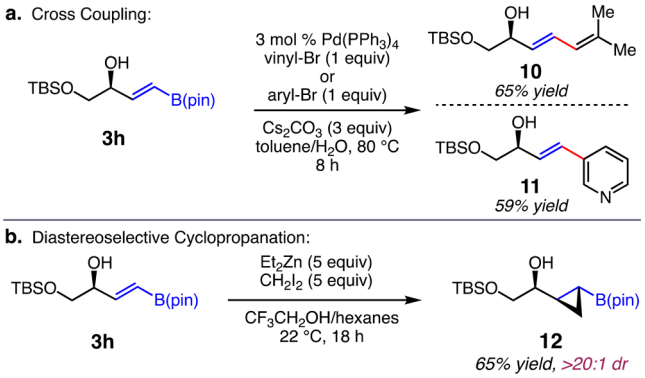
[a]NMR yield. [b]Deprotonation of **8** with LTMP (THF, 0 °C, 30 min) proceeds to 65% conversion (see Supporting Information for details).[14]

ring-opened, albeit less efficiently compared to an epoxide, by carbanion **1** to form the corresponding six-membered ring chelate that is reactive enough to undergo C−B(pin) transmetalation to Pd and subsequent β-hydride elimination. In this regard, under standard conditions, 1 equiv of **6** affords homoallylic alcohol **7** in 20% NMR yield (>20:1 E/Z). Notably, the use of excess oxetane (5 equiv), compared to **1**, in order to assist ring opening did not lead to an increase in reaction efficiency or yield. Second, we hypothesized that exchanging one of the B(pin) groups in **1** with $SiMe_3$ to the corresponding mixed B/Si reagent **8**[13] would enable the stereoselective generation of (E)-alkenylsilanes, providing C−B(pin) transmetalation occurs faster than the alternative 1,4-Brook rearrangement. Deprotonation of **8** with LTMP (THF, 0 °C, 30 min) and sequential treatment with **2** followed by catalytic Pd and allyl chloride results in the formation of **9** in 20% yield (>20:1 E/Z) and 23% of product derived from epoxide opening. Notably, while the reaction is low yielding, the vinylsilane is the only observable alkenylation product (>98:2 Si/B), indicating that loss of the B(pin) unit is kinetically faster than the corresponding dehydrosilylation.

To gain insight into the low conversion to **9**, ^{1}H NMR analysis of the epoxide opening step was investigated (Scheme 3). Treatment of **8** with LTMP followed by **2** results in 59% conversion to cyclic borates **C**/**D** in 1.7:1 dr in addition to 32% unreacted **2**. Of note, the ratio of A/B did not change with temperature. Attempts to follow the reaction after the addition of 5 mol % of Pd and allyl chloride resulted in a complex mixture, where the amounts of both diastereoisomers **C** and **D** decrease, vinylsilane begins to form, but a number unidentifiable resonances are present. While epoxide opening does not seem to be a problem, further studies to understand the details of this process are ongoing.

The (E)-alkenyl boronate allylic alcohols generated through the described protocol can be functionalized in a variety of ways. The examples shown in Scheme 4 are illustrative: (1) The

Scheme 4. Utility of Alkenyl Boronic Ester Products



unprotected allylic alcohol **3h** undergoes palladium-catalyzed cross-coupling in the presence of 3 mol % of $Pd(PPh_3)_4$, Cs_2CO_3, and aryl or alkenyl bromides in toluene for 8 h to afford the 1,3-diene **10** and alkenylpyridine **11** in 65 and 59% yields, respectively. (2) The hydroxyl moiety can also be used to direct vinylboron functionalization.[15] For example, subjection of alkenyl boronic ester **3h** to Simmons−Smith cyclopropanation conditions reported by Shi [Et_2Zn (5 equiv), CH_2I_2 (5 equiv), CF_3CH_2OH, 22 °C, 18 h][16] results in an alcohol-directed cyclopropanation to furnish cyclopropyl boronic ester **12** in 65% yield and >20:1 dr.

In summary, we have developed a practical and robust Pd-catalyzed method for the stereoselective synthesis of (E)-alkenylborons via a coupling/dehydroboration of readily accessible chiral epoxides. Transformations proceed efficiently to furnish di- and trisubstituted alkenyl boronates in good yield and >20:1 E/Z selectivity. Further investigations of stereoselective 1,1-diboron coupling processes are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03853.

Experimental procedures and spectral and analytical data for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Institutes of Health (R01GM116987, 3R01GM116987-01S1) and the University of North Carolina at Chapel Hill. AllyChem is acknowledged for donations of $B_2(pin)_2$.

DOI: 10.1021/acs.orglett.7b03853
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(12) Allyl acetate can be used in place of allyl chloride but results in slightly lower efficiency; for example, 2.5 mol % of $[Pd(Cl)(\eta^3\text{-}C_3H_5)]_2$ and allyl acetate (3 equiv) afford 54% conversion.

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DOI: 10.1021/acs.orglett.7b03853
Org. Lett. XXXX, XXX, XXX−XXX