

Allene Hydroboration

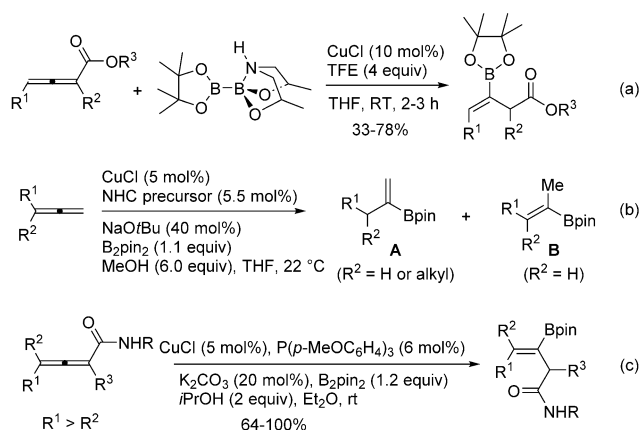
Olefin-Directed Palladium-Catalyzed Regio- and Stereoselective Hydroboration of Allenes

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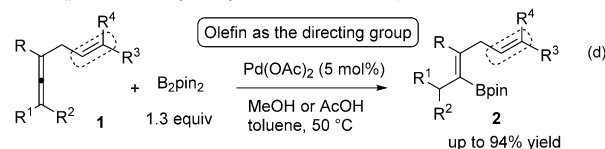
Abstract: An olefin-directed palladium-catalyzed regio- and stereoselective hydroboration of allenes has been developed to afford fully substituted alkenylboron compounds. The reaction showed a broad substrate scope: a number of functionalized allenes, including 2,3-dienoate, 3,4-dienoate, 3,4-dienol, 1,2-allenylphosphonate, and alkyl-substituted allenes, could be used in this olefin-directed allene hydroboration. The olefin unit was proven to be an indispensable element for this transformation.

Organoboranes are a class of highly useful building blocks for the construction of complex molecules in organic synthesis.^[1,2] They have attracted considerable attention and found wide applications in various carbon–carbon bond-forming reactions, such as the Suzuki cross-coupling reaction,^[3,4] and transition-metal-catalyzed 1,2-/1,4-additions.^[5] Selective monohydroboration of allenes,^[6,7] in principle, could be an efficient approach to afford organoboranes.^[8] However, the challenge will be the control of the regio- and stereoselectivity involved in the reaction.^[9] In recent years, copper-catalyzed selective hydroboration of allenes has emerged as an effective strategy for the construction of useful organoboranes.^[9,10] In 2011, Santos and co-workers first reported the copper-catalyzed borylation of 2,3-dienoates (Scheme 1a). In this reaction, a preactivated di-boron reagent is required to produce vinyl boronic esters in moderate yields (33–78%).^[10a] Moreover, Hoveyda et al. developed NHC–Cu-catalyzed hydroboration of monosubstituted allenes with ligand-controlled site selectivity to afford vinyl boronates **A** and **B** respectively (Scheme 1b).^[10b] In addition, enantioselective formation of type-**A** product from 1,1-disubstituted allenes was described (Scheme 1b).^[10c] In 2013, Ma and co-workers reported a highly selective amide-controlled catalytic borylation of allenes proceeding by means of borylcupration. Amide was needed as the directing group to control the site selectivity, thus alkenyl boronates could be obtained from 2,3-dienamide.^[10d] Herein, we wish to disclose our observation on olefin-directed palladium-catalyzed regio- and stereoselective hydroboration of allenes, in which the olefin unit was indispen-

Previous reports on copper-catalyzed hydroboration of allenes:



This work (palladium-catalyzed hydroboration of allenes):



Scheme 1. Previous reports and this approach.

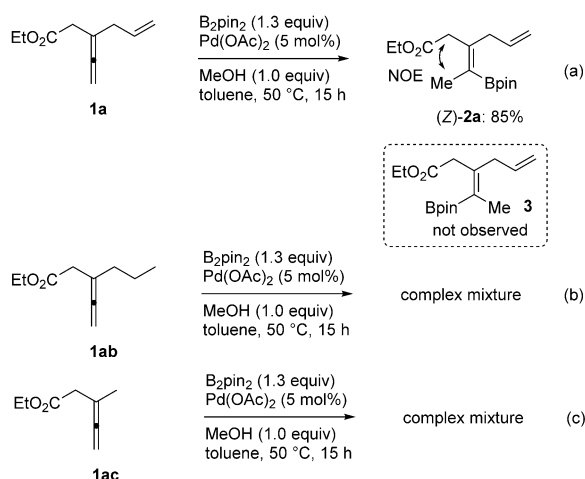
sable in controlling the exclusive selectivity. To the best of our knowledge, there is no report on the palladium-catalyzed highly selective hydroboration of allenes.

We initially chose an easily accessible 3,4-dienoate as the standard substrate.^[11] When allyl-substituted 3,4-dienoate **1a** was treated with B_2pin_2 (1.3 equiv) and MeOH (1.0 equiv) in the presence of $Pd(OAc)_2$ (5 mol%) in toluene at 50 °C for 15 h, inspiring, the hydroborylated product (*Z*)-**2a** was observed in 85% yield as a single regio- and stereoisomer (Scheme 2a). The stereochemistry was determined by NOE measurements.^[12] The exclusive stereoselectivity for the (*Z*)-isomer in this hydroborylative transformation implies a coordination of the olefin group during the reaction.^[13] Comparative experiments were carried out using 3,4-dienoate **1ab** with a propyl-substituent, or **1ac** with a smaller methyl substituent instead of the allyl group; however, only complex reaction mixtures were obtained (Scheme 2b,c; for details see the Supporting Information). These observations indicate that the olefin unit is required as a directing group in this regio- and stereoselective hydroboration of allenes. Thus, coordination of the olefin unit to the palladium center during the reaction would account for the exclusive stereoselectivity of the (*Z*)-isomer.

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Scheme 2. Comparative experiments using different substituents on allenes for the Pd-catalyzed allene-hydroboration. In reaction b, **1ab** was recovered in 6% yield as determined by ¹H NMR using anisole as the internal standard.

With these results in hand, we next examined the scope of allenes **1** in the hydroborylative transformation. First, 2,3-dienolate **1b**, as well as tosyl 3,4-dienol **1c** reacted well and produced the corresponding vinyl boronates in good yields with methanol as the proton source (method A, Table 1, entries 2 and 3). It is interesting to observe that the reaction of 1,2-allenylphosphonate **1d** using method A produced **2d** in only 39% yield, probably due to the high electron-deficiency of the allene moiety (entry 4).^[14] However, the use of 1.0 equivalents of AcOH (method B), in place of MeOH as the proton source,^[15] improved the yield of **2d** dramatically to 90%. Trisubstituted allenes could also be employed with method A, affording products **2e** and **2f** in 74 and 77% yields, respectively (entries 5 and 6). The reaction of fully-substituted allenes **1g** and **1h** failed with method A, but reacted well using 0.8 equivalents of AcOH (method C) as the proton source to give product **2g** and **2h** in good yields (entries 7 and 8). It is worth noting that cycloalkylidene allenes also exhibited good reactivity with method C (entries 9 and 10). To our delight, phenyl or two methyl substituents on the olefin moiety turned out to be compatible with the hydroboration reaction (entries 11 and 12). Further studies showed that *n*Bu and benzyl-substituted allenes performed excellently in this hydroborylative transformation, thus producing the corresponding vinyl boronates **2m** and **2n** in 87 and 91% yield, respectively (entries 13 and 14). Hydroboration of 1,1-disubstituted allene **1o**, in which the allyl group is significantly larger than the other substituent (3,3-dimethylallyl vs. propyl), afforded only product **2o** in 78% yield, strongly supporting the directing effect of the olefin group (Table 1, entry 15). The stereochemistry of **2n** and **2o** was further confirmed by NOE measurements (for details, see the Supporting Information). Finally, the reaction of **1n** with B₂pin₂ was carried out on a one-gram scale to afford **2n** in 94% yield (Scheme 3).

To demonstrate the utility of this highly regio- and stereoselective hydroboration reaction, the transformations in

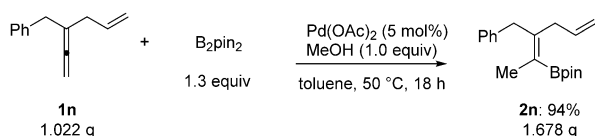
Table 1. Substrate scope the olefin-directed palladium-catalyzed regio- and stereoselective hydroboration of allenes **1**.^[a]

Entry	Enallene (1)	Product (2)	t [h]	Yield of 2 [%] ^[b,c]
1			15	85 (method A)
2			19	87 (method A)
3			17	81 (method A)
4			20	39 (method A) ^[d] 90 (method B)
5			38	74 (method A)
6			19	77 (method A)
7			18	9 (method A) ^[e] 43 (method B) 60 (method C)
8			20	71 (method C)
9			18	70 (method C)
10			18	64 (method C)
11			17	58 (method C)
12			24	74 (method B)

Table 1. (Continued)

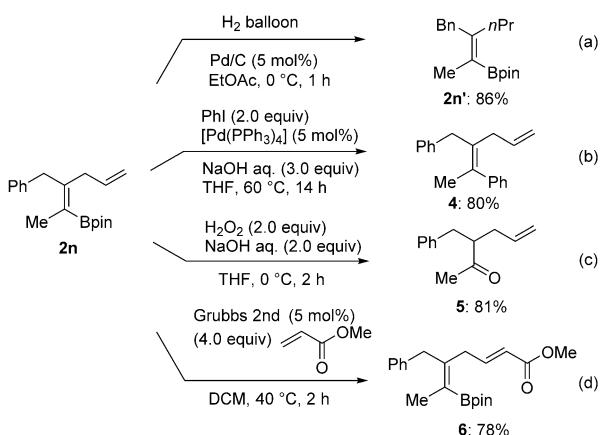
Entry	Enallene (1)	Product (2)	t [h]	Yield of 2 [%] ^[b,c]
13			14	87 (method A)
14			15	91 (method A)
15			10	78 (method A)

[a] The reaction was conducted with Pd(OAc)₂ (5 mol%), B₂pin₂ (1.3 equiv), allene **1** (1.0 equiv), and proton source (indicated in different methods) in toluene at 50 °C. [b] Proton source used in method A: MeOH (1.0 equiv); method B: AcOH (1.0 equiv); method C: AcOH (0.8 equiv). [c] Isolated yield. [d] **1d** was recovered in 52% yield as determined by ¹H NMR using anisole as the internal standard. [e] **1g** was recovered in 53% yield as determined by ¹H NMR using anisole as the internal standard.



Scheme 3. Gram-scale synthesis of **2n** from **1n**.

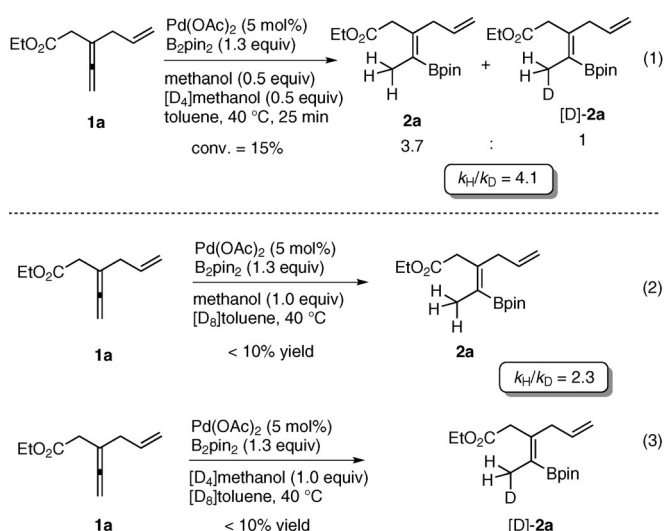
Scheme 4 were carried out. Selective hydrogenation of the carbon–carbon double bond on the allyl moiety gave reduced fully-substituted vinyl boronate **2n'** in 86% yield. Suzuki cou-



Scheme 4. Versatile transformations of the hydroborylated product **2n** (Grubbs 2nd=Grubbs second-generation Ru catalyst).

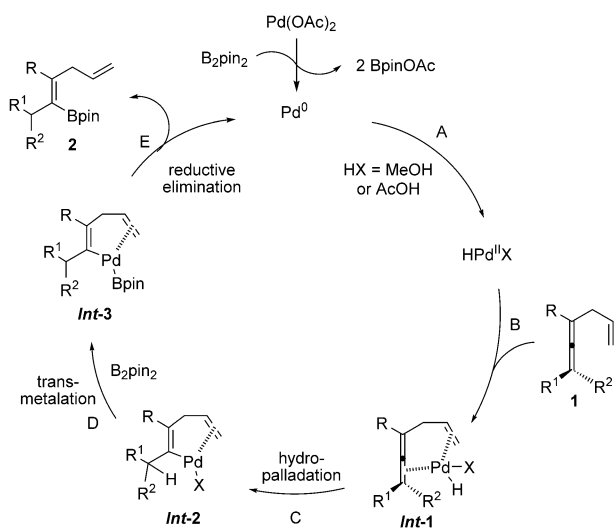
pling of vinyl boronate **2n** with iodobenzene afforded product **4** in 80% yield without loss of geometrical purity.^[10g] Furthermore, hydroxylation of **2n** could also be conducted to give γ,δ -unsaturated methyl ketone **5** in 81% yield.^[10g] Cross-metathesis of **2n** with methyl acrylate promoted by Grubbs II catalyst produced **6** in 78% yield with complete *E* selectivity (Scheme 4).^[16]

To gain a deeper insight into the allene hydroboration, mechanistic studies on kinetic isotope effects (KIE) were done. An intermolecular competition experiment was carried out using a 1:1 mixture of methanol and [D₄]methanol at 40 °C for 25 min [Eq. (1)]. The product ratio **2a**/[D]-**2a** (ca. 15% conv.) was measured as 3.7:1. On the basis of this ratio, the competitive KIE was calculated to be $k_H/k_D=4.1$.^[17] Furthermore, in parallel experiments (from initial rate) a KIE of $k_H/k_D=2.3$ was obtained [Eqs. (2) and (3)].^[17]



Based on the mechanistic studies, the stereochemical outcome, and the comparative experiments in Scheme 2, a possible mechanism for the allene hydroboration is proposed in Scheme 5. Pd⁰ is most likely formed from reaction with B₂pin₂, and protonation of the Pd⁰ intermediate by methanol or acetic acid would produce a Pd-hydride (Scheme 5, step A).^[15,18] Simultaneous coordination of the allyl C=C bond and the allenyl C=C bond of substrate **1** to the Pd^{II} center would promote the formation of **Int-1** (step B).^[19] Subsequent hydrometallation of the allene in **Int-1** would give vinylpalladium intermediate **Int-2** (step C). The coordination of olefin to Pd^{II} would account for a *cis* orientation of Pd^{II} and the allyl group. Transmetalation of **Int-2** with B₂pin₂ would produce **Int-3** (step D), which on subsequent reductive elimination (step E) would lead to vinyl boronate **2**. Here, it is worth noting that this palladium-catalyzed hydroboration proceeds via hydrometallation and subsequent borylation, instead of borylmethylation/protonation, which is usually observed in copper-catalyzed reactions.^[20]

Since H-transfer takes place in two different steps in Scheme 5, that is, proton transfer in step A and hydride transfer in step C, the deuterium isotope effects from Equations



Scheme 5. Proposed mechanism for the olefin-directed palladium-catalyzed regio- and stereoselective hydroboration of allenes.

(1–3) could arise from either of these steps or both. The data from the parallel experiments [Eqs. (2) and (3)] cannot distinguish which of the steps A or C is rate-limiting. From the competitive experiment [Eq. (1)] one can conclude that at least one of the H-transfer steps (A or C) has to be irreversible.^[21] If both of these steps are irreversible the isotope effect $k_H/k_D = 4.1$ will arise from both steps A and C.^[22]

In conclusion, we have developed an efficient olefin-directed palladium-catalyzed regio- and stereoselective hydroboration of allenes under mild conditions. The reaction proceeds via hydro-palladation and subsequent borylation. Furthermore, the reaction showed a broad substrate scope for various functionalized allenes, including 2,3-dienoate, 3,4-dienoate, 3,4-dienol, 1,2-allenylphosphonate, and alkyl-substituted allenes. Comparative experiments showed that the olefin is an indispensable directing group for the regio- and stereoselective formation of vinyl boronates. Finally, due to the success of our approach in the selective synthesis of fully substituted alkenylborons, this method will be highly attractive for organic and medicinal chemists. Further studies in this area, including synthetic applications are currently underway in our laboratory.

Acknowledgements

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Keywords: allenes • directing group • hydroboration • olefin • palladium

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- [22] If both steps A and C are irreversible there would be a first selection at step A [$(k_H/k_D)_A$] giving a preference of Pd–H over Pd–D. This ratio continues to step C and if the latter step is also irreversible there would be a second selection [$(k_H/k_D)_C$] of Pd–H over Pd–D in the insertion. Thus, in this case, the competitive isotope effect would be $k_H/k_D = (k_H/k_D)_A \times (k_H/k_D)_C$.

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