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Catalytic Carbo- and Aminoboration of Alkenyl Carbonyl Compounds via 5- and 6-Membered Palladacycles

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Abstract

A palladium(II)-catalyzed alkene difunctionalization reaction has been developed, wherein B₂pin₂ is used to trap chelation-stabilized alkylpalladium(II) intermediates that are formed upon nucleopalladation. A range of carbon and nitrogen nucleophiles were found to be suitable coupling partners in this transformation, providing moderate to high yields. Both 3-butenic and 4-pentenic acid derivatives were reactive substrate classes, affording β, γ- and γ,δ-difunctionalized carboxylic acid derivatives. This work represents a new strategy to synthesize highly functionalized secondary boronates that complements existing methods.

Graphical Abstract

Organoboron compounds are valuable synthetic intermediates due to their ability to participate in a variety of C–C and C–heteroatom bond-forming reactions.¹ They have also been widely used in material science and drug discovery.² Numerous methods have been developed to prepare organoborons, including metal-catalyzed borylation of organohalides, hydroboration of C–C π -bonds, and oxidative borylation of C–H bonds.³ Among these approaches, alkene difunctionalization reactions involving boron coupling partners are of particular interest because they enable rapid generation of molecular complexity and enable construction of two adjacent stereocenters, including at least one C(sp³)–B stereocenter. Significant efforts have been made to achieve borylative 1,2-difunctionalization during the past decade, as pioneered by Morken, Miura, Nakao, Brown and others.^{4,5} Most existing catalytic alkene carbo- and aminoboration reactions involve copper–boryl intermediates that

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Notes

The authors declare no competing financial interest.

Supporting Information

Experiment details, spectra data, copies of ¹H and ¹³C NMR spectra, and X-ray crystallographic data. These materials are available free of charge via the Internet at <http://pubs.acs.org>.

react via *syn*-1,2-migratory insertion into C–C π -bonds. By contrast, palladium-catalyzed variants, which offer the potential for *anti*-selectivity and distinct coupling partner scope, remain underdeveloped.

Recently, our group has successfully demonstrated palladium-catalyzed intermolecular 1,2-dicarbofunctionalization and carboamination reactions via a directed nucleopalladation strategy (Scheme 1A).^{6,7} By intercepting a chelation-stabilized 5-membered nucleopalladated intermediate with a carbon electrophile along a Pd(II)/Pd(IV) redox manifold, we have achieved 1,2-difunctionalization of 3-butenic acid derivatives. In light of the potential utility of analogous reactions involving boron coupling partners, we questioned whether nucleopalladated Wacker-type intermediates could be intercepted via transmetalation with a nucleophilic boron source, such as B₂pin₂, as a strategy for borylative alkene difunctionalization (Scheme 1B). We envisioned that such a process would proceed via a Pd(II)/Pd(0) cycle involving C(sp³)–B reductive elimination and reoxidation, which would be mechanistically distinct from previous work. Notably, the feasibility of intercepting alkylpalladium(II) intermediates with B₂pin₂ has been previously demonstrated in the C–H activation field by Shi and Yu.⁸ To the best of our knowledge, intermolecular palladium(II)-catalyzed 1,2-carbo- and aminoboration reactions of alkenes have not been previously reported. At the outset, we recognized that several challenges would need to be overcome to reduce this idea to practice, including identifying reaction conditions in which the three reacting components are mutually compatible, achieving appropriate rates of each elementary step in the proposed cycle, and controlling regio-, stereo-, and 1,2-versus-1,1-selectivity. Herein, we describe the realization of this goal through the development of catalytic, directed borylative 1,2-difunctionalization of non-conjugated alkenes with a variety of carbon and nitrogen nucleophiles. This mode of reactivity enables reactivity through both 5- and 6-membered palladacycle intermediates. In this way, boron can be installed at the γ position relative to a carbonyl group, which cannot be accomplished through existing C(sp³)–H borylation methods.^{8,9}

To initiate our study, we selected 8-aminoquinoline¹⁰ (AQ)-masked 3-butenic acid as our pilot alkene substrate (**1a**), *N*-methylindole (**2a**) as the nucleophile, and B₂pin₂ as the boron source (**3a**) (Table 1). After extensive screening of different bases, solvents and external oxidants, we found that using KF as the base, O₂ and catalytic 1,4-benzoquinone (BQ) as oxidants at 60 °C, the 1,2-carboborylated product **4a** could be isolated in 80% yield. Notably, this reaction also proceeds at 45 °C, providing similar yield with *N*-methyl indole (**2a**) as the nucleophile (See Supporting Information (SI) for optimization details). We then tested the scope of carbon nucleophiles with alkene substrate **1a** and B₂pin₂ (**3a**). To our delight, indoles (**2a** and **2b**), methyl cyanoacetate (**2c**) and a 1,3-dicarbonyl compound (**2d**) all proved to be suitable nucleophiles, providing the corresponding products in moderate to good yields (**4a–4d**). A variety of substituted alkene substrates (**1b–1f**) are well tolerated in this reaction. Mono- α -substituted substrates underwent this transformation in good yields and with >20:1 d.r. (**4e** and **4f**). Internal linear (**4h**) and cyclic (**4g**) alkenes were 1,2-carboborylated under the optimized conditions, establishing two new stereocenters in a single operation. The relative stereochemistry of **4g** establishes that the reaction proceeds in an *anti* fashion. With dialkyl internal alkenes, the low d.r. is attributed to starting material

E/Z-isomerization.⁶ Interestingly, when *E*-styrenyl substrates (**1f–1h**) were subjected to the reaction conditions, we observed formation of both possible regioisomers, with the major product corresponding to the 6-membered palladacycle intermediate (**4i'–4k'**) (*vide infra*). This result is presumably due to the intermediacy of a stabilized benzylpalladium(II) upon 6-membered carbopalladation. Additionally, alkene polarization also appears to play a role, as an electron-withdrawing *para*-cyano group (**1f**) provided higher selectivity than an electron-donating *para*-methoxy group (**1h**).

Next, we investigated the compatibility of nitrogen nucleophiles in this transformation (Table 2). Under the reaction conditions in Table 1, however, no desired product was formed when phthalimide (**2e**) was employed as the nucleophile. We have previously established that nucleopalladation with nitrogen-based nucleophiles is less facile than with carbon-based nucleophiles,⁷ which prompted us to investigate more forcing reaction conditions. Extensive experimentation ultimately led to optimal conditions for nitrogen nucleophiles: 100 °C, 2,6-dimethyl benzoquinone (DMBQ) as the oxidant, and KHCO₃ as the base. An inert (N₂) atmosphere is required to prevent competitive 1,2-aminohydroxylation; carbon nucleophiles appear not to undergo this pathway for reasons that remain unclear. Similar to the previously reported C–H borylation reaction,^{8b} TEABF₄ was also found to be a beneficial additive to improve the yield (See Supporting Information (SI) for optimization details).

Having optimized the reaction conditions, we next investigated the substrate scope of this palladium(II)-catalyzed alkene 1,2-aminoboration reaction (Table 2). First, different nitrogen nucleophiles (**2e–l**) were tested with alkene substrate **1a** and B₂pin₂ (**3a**). Masked ammonia nucleophiles (**6a–6d** and **6f**) and hydroxamic acid derivatives (**6g** and **6h**) were found to be compatible coupling partners, giving moderate to good yields. Many of these nitrogen nucleophiles can be conveniently converted to primary amines upon deprotection. Alkene substrates bearing an α -substituent are suitable for this reaction (**6i** and **6j**), though the diastereoselectivity was low in these cases, possibly due to the high reaction temperature. With an internal alkene substrate (**1e**), the reaction proceeded in lower yield and requires higher catalyst loading (**6k**). A plausible explanation for this observation is that the aminopalladation step becomes much energetically unfavorable due to enhanced steric repulsion. Notably, the pinacol boronate products can be easily transformed to 1,2-aminoalcohols (**6a–6k**), an important structural motif for synthetic and medicinal chemistry, under mild oxidation conditions.

A limitation of our previously published directed alkene functionalization reactions is that they have been restricted to alkene substrates capable of forming a 5-membered metallacycle upon nucleometalation.^{6,7,11} Substrates with more distal alkenes form larger metalacycles, which are less stable and short-lived under the reaction conditions due to competitive β -hydride elimination.¹¹ We envisioned that in the present reaction, transmetalation with B₂pin₂ may be sufficiently fast to enable compatibility with a 6-membered palladacycle.¹² Such a strategy would be distinct from and complementary to our recent efforts to develop directing groups to stabilize larger palladacycles.¹³

Indeed, we observed that both carboboration and aminoboration reactions were compatible with 4-pentenoic acid derivatives under slightly modified conditions (Table 3). Alkene

substrates bearing an α - or β -substituent (**1k** and **1l**) are tolerated in this transformation. The comparatively low d.r. values in these cases are likely due to the more flexible nature of the 6-membered palladacycle intermediate. It is noted that protected allyl glycine could be aminoborylated in moderate yield, affording a biologically interesting and modifiable amino acid structure. We were pleased to find that different carbon nucleophiles (**2i–2k**) also underwent this transformation smoothly.¹⁴ However, both methods were incompatible with internal distal alkenes, potentially due to steric hindrance, which increases the energy barrier for the nucleopalladation and reductive elimination steps.

Subsequently, we conducted large-scale reactions of the Pd(II)-catalyzed alkene aminoboration method to demonstrate the practicality and operational simplicity of this methodology (Scheme 2). Alkene substrates **1a** and **1j** were aminoborylated to give **5b** and **7d** in 91% and 65% isolated yields respectively.

To further illustrate the synthetic utility of the difunctionalized products, a series of transformations of the alkyl pinacol boronate were performed (Scheme 3). After oxidation of the aminoborylated product **7d**, the hydroxyl group was protected to form silyl ether **8**. The aminohydroxylated intermediate could be cyclized to form a five-membered lactone **9** under acidic conditions at 120 °C, which simultaneously removes the 8-aminoquinoline directing group. To our delight, the boron group could also be transformed into different halogen atoms. Treating the oxidized product **6a** with thionyl chloride gives the β -chlorinated compound **10** in moderate yield.¹⁵ Direct fluorination of the aminoborylated product **5a** in the presence of AgNO₃ and Selectfluor proceeded successfully to yield compound **11**,¹⁶ albeit in low yield. Furthermore, pinacol boronate **5b** was converted into the trifluoroborate salt **12** in 90% yield when treated with aqueous KHF₂ solution. Alkyl trifluoroborate salts have been widely used in Suzuki–Miyaura cross-coupling.¹⁷ Finally, global deprotection of **5b** could be conveniently carried out with the retention of C–B bond by treatment with 6 M HCl under inert atmosphere, affording β -borono- γ -amino acid **13** in high yield.

A plausible mechanism for this Pd(II)-catalyzed alkene difunctionalization reaction is proposed in Scheme 4. After the directing group binds to the palladium catalyst, nucleopalladation of the alkene substrates will generate a 5- or 6-membered palladacycle. Next, transmetalation with B₂Pin₂ occurs with the assistance of base, followed by reductive elimination to forge the carbon–boron bond and form palladium(0). The external oxidants in the reaction system oxidize Pd(0) to regenerate the active Pd(II) catalyst, closing the catalytic cycle.⁸ For the 6-membered palladacycle, it is less stable and not as long-lived as the 5-membered intermediate. However, in our reaction system, the boron group transmetalation or Pd(II) reductive elimination step is sufficiently rapid to outcompete the problematic β -hydride elimination pathway.

In conclusion, we have developed regiocontrolled carbo- and aminoboration reactions of non-conjugated alkenes using a cleavable 8-aminoquinoline (AQ) directing group. By using B₂pin₂ as the transmetalating reagent, we have successfully installed a boron group to the carbonyl β and γ positions through 5- and 6-membered palladacycle intermediates. To our knowledge, this work represents the first example of palladium(II)-catalyzed catalytic alkene 1,2-difunctionalization involving a diboron coupling partner. The reactions proceeded

smoothly with a broad range of carbon and nitrogen nucleophiles as well as sterically hindered internal and α -substituted alkene substrates. The reactions are scalable and operationally simple. We have also demonstrated the synthetic utility of pinacol boronate through five different diversifications. Future investigation will focus on elucidating the reaction mechanism and expanding this borylation chemistry to more general alkene substrates. These results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A. Previous work: Pd(II)/Pd(IV) cycle, only 5-membered palladacycle **B. This work: Pd(II)/Pd(0) cycle, 5- and 6-membered palladacycles**

Scheme 1.
Background and Project Synopsis

Scheme 2.
Large-Scale Synthesis

Scheme 3.
Diversification of Aminoborylated Products

Scheme 4.
Proposed Reaction Mechanism

Table 1

Alkene Carboboration Scope

^aReaction conditions **A**: Alkene substrate (0.1 mmol), **2a** (1.5 equiv), **3a** (2 equiv), Pd(OAc)₂ (5 mol%), BQ (10 mol%), KF (1 equiv), HFIP (0.1 mL), 60 °C, O₂, 16–20 h.

^bReaction conditions **B**: Alkene substrate (0.1 mmol), **2a-d** (3 equiv), **3a** (4 equiv), Pd(OAc)₂ (10 mol%), BQ (20 mol%), KF (2 equiv), HFIP (0.2 mL), 60 °C, O₂, 16–20 h. Percentages refer to the isolated yields.

^c*E*-alkene starting material was used.

Table 2

Alkene Aminoboration Scope^a

^aReaction conditions: Alkene substrates (0.1 mmol), 2e-l (1.5 equiv), 3a (2 equiv), Pd(OAc)₂ (10 mol%), KHCO₃ (1 equiv), DMBQ (1.3 equiv), TEABF₄ (0.5 equiv), PhCN (0.2 mL), 100 °C, N₂, 6 h. Percentages refer to isolated yields.

^bd.r. = 3.6:1 prior to oxidation (¹H NMR of crude reaction mixture)

^c20 mol% Pd(OAc)₂, 24 h; *E*-alkene starting material was used.

Table 3

 γ,δ -Difunctionalization of Carboxylic Acid Derivatives

^aReaction conditions **A**: **1j** (0.1 mmol), **2a-c** (3 equiv), **3a** (4 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol%), BQ (20 mol%), KF (2 equiv), HFIP (0.2 mL), 60 °C, O_2 , 16–20 h.

^bReaction conditions **B**: **1j-l** (0.1 mmol), **2e** (1.5 equiv), **3a** (2 equiv), $\text{Pd}(\text{OAc})_2$ (20 mol%), KHCO_3 (1 equiv), DMBQ (1.3 equiv), TEABF₄ (0.5 equiv), PhCN (0.2 mL), 100 °C, N_2 , 16–20 h. Percentages refer to isolated yields.