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Palladium-Catalyzed 1,3-Difunctionalization using Terminal Alkenes with Alkenyl Nonaflates and Aryl Boronic Acids

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Abstract

A Pd-catalyzed 1,3-difunctionalization of terminal alkenes using 1,1-disubstituted alkenyl nonaflates and arylboronic acid coupling partners is reported. This transformation affords allylic arene products that are difficult to selectively access using traditional Heck cross-coupling methodologies. The evaluation of seldom employed 1,1-disubstituted alkenyl nonaflate coupling partners led to the elucidation of subtle mechanistic features of π -allyl stabilized Pd-intermediates. Good stereo- and regioselectivity for the formation of 1,3-addition products can be accessed through a minimization of steric interactions that emanate from alkenyl nonaflate substitution.

Graphical abstract

The utility of π -allyl species has been demonstrated as an indispensable method for stabilizing Pd-intermediates from undergoing undesired reaction pathways.¹ Furthermore, the use of these stabilized intermediates in Pd-catalyzed alkene difunctionalization reactions has been reported in an array of transformations.² Despite these reports, the implications of electronic or steric influences on the C-2 position of π -allyl stabilized reaction intermediates remain relatively difficult to explore with high efficiency. Therefore, we aimed to develop a difunctionalization reaction of terminal alkenes^{2e-f} (**1**) that provided the ability to tune electronic and/or steric effects on π -allyl intermediates with modularity (Scheme 1A). In this regard, we sought to employ 1,1-disubstituted alkenyl nonaflates³⁻⁴ (**2**) with various R¹-groups as a means to simultaneously investigate subtle mechanistic attributes of the C-2 position on π -allyl intermediates as well as to afford a unique class of 1,3-alkene difunctionalization products (**4**). The successful development of a 1,3-addition reaction of this type would generate allylic arene scaffolds, which are difficult to access using traditional Heck approaches.⁵ Furthermore, the use of readily available terminal alkene

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Supporting Information

Experimental procedures and full spectroscopic data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

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coupling partners would provide access to allylic arene products with increased molecular complexity in a complementary approach to allylic cross-coupling methods.⁶

Recently, we have reported a highly selective Pd-catalyzed 1,1-alkene difunctionalization of the commodity chemical ethylene using cyclic alkenyl triflates/nonaflates and arylboronic acids (Scheme 1B).^{2f} While generally high selectivity was observed for 1,1-addition products, a 1,3-addition product was periodically detected as the result of π -allyl isomerization (vide infra). We proposed that the formation of an exocyclic alkene thermodynamically disfavored the formation of the 1,3-addition product. Using a similar approach, we hypothesized that an acyclic 1,1-disubstituted alkenyl nonaflate (**2**) could be utilized to selectively access the previously unattainable 1,3-addition product (**4**). While the presence of a terminal alkene in alkenyl nonaflate **2** could present challenges if it were to participate in Heck-type side reactions, we hypothesized the electron-deficient character, relative to alkene **1**, would restrict this undesired reactivity. Mechanistically, this transformation would initiate with the oxidative addition of an alkenyl nonaflate (**2**) to generate cationic Pd-intermediate **A**,⁷ which undergoes selective alkene migratory insertion to afford alkyl-Pd intermediate **B** (Scheme 1C). We propose the relative rate of migratory insertion out competes the Suzuki cross-coupling pathway due to the cationic nature of Pd-intermediate **A**, that results from the poorly coordinating nonaflate counterion.^{1e,2f-i} Subsequent β -hydride elimination of alkyl-Pd intermediate **B** would result in the formation of the 1,3-diene coordinated Pdhydride intermediate (**C**). As previous studies suggest, facile reinsertion of the 1,3-diene into the Pd-H bond is likely prompted by the formation of the π -allyl stabilized intermediate **D**.^{2e-f,8} The 1,3-addition product **4** would be generated following transmetalation of an arylboronic acid and selective reductive elimination at the C-3 position of π -allyl intermediate **D**.

For the development of a highly selective 1,3-difunctionalization, the potential reaction pathways of isomerizing σ - π intermediates as they relate to the π -allyl stabilized Pd-intermediate (**D**) must be considered.⁹ Formation of analogous 1,1-difunctionalization products to that shown in Scheme 1B could result in complex product mixtures if reductive elimination were unselective for the C-1 or C-3 positions of intermediate **D**. We rationalized by transitioning from cyclic alkenyl oxidants to the 1,1-disubstituted alkenyl nonaflate derivatives that the proposed facile σ - π - σ isomerization process (**E**→**D**→**F**, Figure 1) would be favorable due to a reduction of steric interactions at the C-3 position (**F**) relative to the C-1 position (**E**). In addition, examination of the mechanism for π -allyl isomerization reveals that 1,3-addition product **4** can be formed with either *E*- or *Z*-stereochemistry. To avoid confusion as the result of changing stereochemical outcomes for differing R¹-substituents, we have defined an *anti/syn* relationship between olefin substituents H and R¹ (Figure 1).^{2a} The selectivity between these stereoisomers is controlled by a requisite C-C bond rotation that enables access to *anti*-**4** and *syn*-**4** precursors **E** and **G**, respectively.

Starting from previously described reaction conditions,²ⁱ only modest changes were required to afford 1,3-addition product **4** in good yield and selectivity.¹⁰ Optimization studies revealed the importance of coupling partner stoichiometry to minimize the formation of Suzuki cross-coupling side products. Specifically, we found the use of 3.0 equivalents of the terminal alkene created a concentration bias that promoted alkene migratory insertion of Pd-

intermediate **A**, rather than a Suzuki cross-coupling reaction. Using optimized reaction conditions with terminal alkene **1a**, alkenyl triflate **2a**, and phenylboronic acid **3a**, we were pleased to observe excellent product yields (86%) and good regioselectivity (7.8:1) for the desired 1,3-addition product **4a** over the 1,1-addition product **5a** (Figure 2). While the transformation affords 1,3-alkene difunctionalization products with good selectivity, it is important to note that further enriched samples of stereo- or regioisomers can be obtained by performing flash column chromatography on the isomeric mixtures using silica gel impregnated with silver nitrate.¹¹

We sought to evaluate the scope of the transformation beginning with the assessment of various 1,1-disubstituted alkenyl nonaflates (Figure 2). Using terminal alkene **1a** and phenylboronic acid **3b**, moderate to good yields were observed for alkene difunctionalization products that included a variety of R¹-substituents including: methyl (**4a**), hydrogen (**4b**), tetrahydropyran (**4d**), and methyl ester (**4e**). The potential synthetic utility for the transformation is nicely demonstrated with the formation of the highly functionalized allylic arene product **4e**, although the 1,3-addition isomer is produced with only modest regioselectivity. Unfortunately, 1,3-diene alkenyl triflate **2f** was relatively unstable and likely decomposed under the reaction conditions, thus accounting for the low yield of **4f**.

The evaluation of various 1,1-disubstituted alkenyl nonaflates also served to probe mechanistic properties of π -allyl stabilized Pd-intermediates. As discussed above, *anti* and *syn* 1,3-addition products are derived from the σ - π - σ isomerization sequence of π -allyl intermediates (Figure 1).^{1a,1g-1,2k,6f} In Table 1, we observe greater *anti*-**4**:*syn*-**4** selectivity for smaller alkenyl nonaflates R¹-substituents as compared to larger R¹-substituents (*i.e.*, 95:5 for R¹ = H, *versus* 61:39 for R¹ = *i*-Pr). Consistent with the observation of this steric effect, by comparing the logarithm of *anti*-**4**:*syn*-**4** selectivity with Sterimol B₅ values (maximum radius corresponding to the alkenyl nonaflate R¹-substituent)^{12,13} a correlation was observed (Figure 3A). The resultant free energy relationship is suggestive that the relative size of R¹-substituents directly influences isomerization of π -allyl intermediates. In this case, as the R¹-group becomes increasingly large C–C bond rotation of intermediate **E** is increasingly favorable (**D**→**E**→**G**→**H**, Figure 1). The relief of allylic strain between the *anti* and *syn* conformations of the 1,3-addition product **4** is likely responsible for this observed correlation.¹⁴

The regioselectivity between 1,3-(**4**) and 1,1-addition (**5**) products was also affected by the nature of the 1,1-disubstituted alkenyl nonaflates.^{1a,1h,1j-k,6e-f} Decreased selectivity between π -allyl derived products **4** and **5** was observed by changing from phenylboronic acid coupling partner **3a** to the smaller styrenylboronic acid **3l** (vide infra). In addition, greater selectivity for the formation of 1,3-addition product **4** was observed for smaller R¹-substituents relative to alkenyl nonaflate derivatives with larger substituents (*i.e.*, 11:1 for R¹ = H, *versus* 3.1:1 for R¹ = *i*-Pr). The dependence of the regioselectivity on alkenyl nonaflate steric properties was supported by the identification of a second free energy relationship between the logarithm of the regioselectivity and Sterimol B₅ values (Figure 3B).¹³ This correlation is suggestive that the size of R¹-substituents can destabilize reductive elimination precursor σ -allyl intermediate **F**, which in turn favors formation of 1,1-addition product **5**

(through intermediate **E**). Although, **4f** did not coincide with this correlation, it is possible the geminal dimethyl substituted alkene coordinates to palladium, therefore disrupting π -allyl isomerization. Unfortunately, the correlations we observed between reaction outcome and steric descriptors are indicative that for a highly selective 1,3-difunctionalization a relatively limited set of alkenyl nonaflate coupling partners can be employed.

After evaluating the tolerance of alkenyl nonaflate substituents in the formation of allylic arenes **4a–4f**, we focused our efforts on the functional group compatibility of the 1,3-difunctionalization. Various electronically disparate arylboronic acids were tolerated in the formation of 1,3-addition products, including arenes with 4-(HO)C₆H₄ (**4h**), 3-(MeO₂S)C₆H₄ (**4i**), and sterically encumbering 2-MeC₆H₄ (**4n**) substitution (Figure 4). Unfortunately, difunctionalization products with potentially reactive groups, including 4-NO₂C₆H₄ (**4k**) and 4-BrC₆H₄ (**4l**), were formed with reduced product yields, albeit good regioselectivity. While the assessment of arylboronic acids establish adequate regioselectivity between products **4** and **5**, the greatest selectivity was observed for electron-deficient arene coupling partners (*i.e.*, 8.2:1 (**4:5**) for R² = Ph (**4g**), *versus* 19:1 for R² = 4-(NO₂)C₆H₄ (**4k**)). This may be indicative of a subtle sensitivity of the regioselectivity of reductive elimination from π -allyl stabilized intermediate **D** to the electronic properties of the boronic acid coupling partner. Terminal alkenes containing distal primary alcohol (**4p**), cyano (**4q**), and phthalimide (**4r**) functional groups were compatible substrates, affording difunction-alization products in moderate to good product selectivity and yields. Alkenylboronic acid coupling partners could be utilized and offer an attractive extension of this methodology to difficult-to-access skipped diene product motifs (**4s–4v**).¹⁵ The modest product yield of **4v** may be the result of the potentially reactive terminal olefin-containing product being consumed in the reaction.¹⁶ Consistent with results discussed above, the use of 1,1-disubstituted alkenyl nonaflates with either Me or H substitution afforded good selectivity for the *anti*-1,3-addition product **4**.

In summary, we have developed a novel Pd-catalyzed alkene difunctionalization reaction that employs a distinctive 1,1-disubstituted class of alkenyl nonaflate coupling partners to generate 1,3-addition products regioselectively. This transformation represents a unique disconnection strategy for the modular regioselective production of allylic arene or skipped diene molecular architectures in good yields. Through the evaluation of alkenyl nonaflate coupling partners, we identified a significant influence of the steric properties of alkenyl nonaflate substituents on the stereo- and regioselectivity of the reaction. These studies demonstrated a limitation of this methodology is the formation of isomeric mixtures with only modest selectivity when sterically encumbering 1,1-disubstituted alkenyl nonaflate coupling partners are utilized. The identification of these trends will likely impact the development of future alkene difunctionalization reactions in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mechanistic rationale for the formation of regioisomers and *anti/syn* 1,3-difunctionalization products.

Figure 2.

Scope of the Pd-catalyzed 1,3-difunctionalization with assorted 1,1-disubstituted alkenyl nonaflates. Yields are reported as a combination of isomers of reactions performed on a 0.5 mmol scale. Structures of major stereoisomers are shown and were confirmed by NMR analysis. Isomeric ratios were determined by GC analysis of crude product mixture.^a Triflate analog of **2** was used in place of nonaflate.

Figure 3.
 (A) Correlation between *anti* and *syn* 1,3-addition isomers and Sterimol B_5 values. (B)
 Correlation between 1,3- and 1,1-addition regioisomers and Sterimol B_5 values.

Figure 4.

Exploration of the scope of the Pd-catalyzed 1,3-difunctionalization of terminal alkenes.

Yields are reported as a combination of isomers of reactions performed on a 0.5 mmol scale.

Structures of major stereoisomers are shown and were confirmed by NMR analysis.

Isomeric ratios were determined by GC analysis of crude product mixture.

A. Proposed Pd-catalyzed 1,3-difunctionalization of terminal alkenes.

B. Pd-catalyzed 1,1-alkenylarylation of ethylene.

C. Mechanistic hypothesis.

Scheme 1.
Difunctionalization Reactions of Terminal Alkenes