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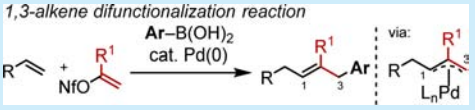
Palladium-Catalyzed 1,3-Difunctionalization Using Terminal Alkenes with Alkenyl Nonaflates and Aryl Boronic Acids

Matthew S. McCammant, Takashi Shigeta, and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112, United States

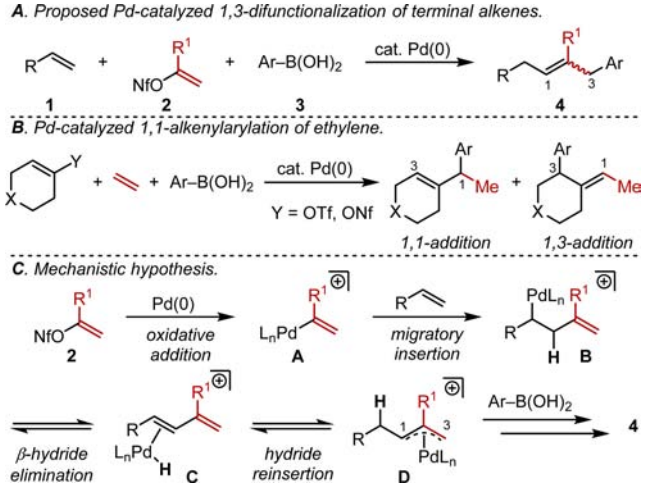
Supporting Information

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.



The utility of π-allyl species has been demonstrated as an indispensible 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 nonaflates[3,4] (**2**) with various R^1-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 coupling partners would provide access to allylic arene products with increased molecular complexity in a complementary approach to allylic cross-coupling methods.[6]

Scheme 1. Difunctionalization Reactions of Terminal Alkenes



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 outcompetes the Suzuki cross-coupling pathway due to the cationic nature of Pd-intermediate **A**, which 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 Pd-hydride 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

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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 $\sigma-\pi$ 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 $\sigma-\pi-\sigma$ isomerization process (**E** → **D** → **F**, Figure 1) would be favorable due to a reduction of steric

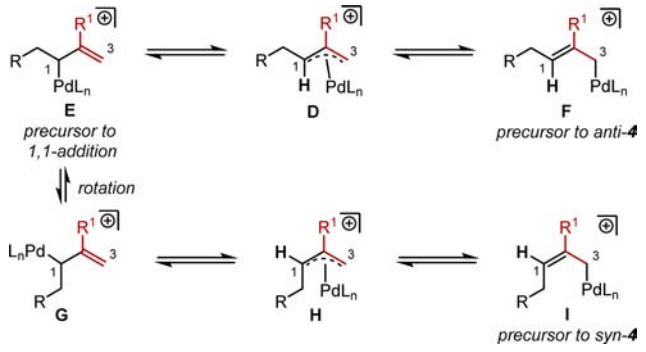

Figure 1. Mechanistic rationale for the formation of regioisomers and *anti*/*syn* 1,3-difunctionalization products.

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 R^1-substituents, we have defined an *anti*/*syn* relationship between olefin substituents H and R^1 (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 equiv 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 **3a**, moderate to good yields were observed for alkene difunctionalization products that included a variety of

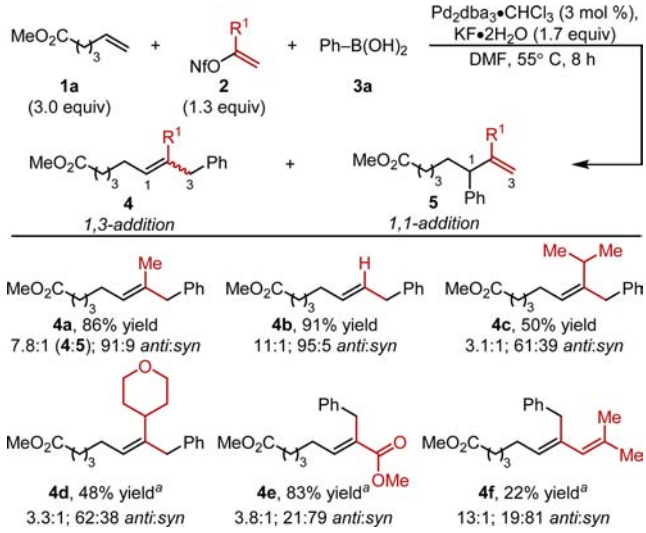

Figure 2. Scope of the Pd-catalyzed 1,3-difunctionalization with assorted 1,1-disubstituted alkenyl nonaflates. Yields are reported as a combination of isomers of reactions performed on a 0.5 mmol scale. Structures of major stereoisomers are shown and were confirmed by NMR analysis. Isomeric ratios were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

R^1-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 $\sigma-\pi-\sigma$ isomerization sequence of π-allyl intermediates (Figure 1).[1a,g−i,2k,6f] In Figure 2, we observe greater *anti*-**4**/*syn*-**4** selectivity for smaller alkenyl nonaflate R^1-substituents as compared to larger R^1-substituents (i.e., 95:5 for R^1 = H, versus 61:39 for R^1 = *i*-Pr). Consistent with the observation of this steric effect, by comparing the logarithm of *anti*-**4**/*syn*-**4** selectivity with Sterimol B_5 values (maximum radius corresponding to the alkenyl nonaflate R^1-substituent)[12,13] a correlation was observed (Figure 3A). The resultant free energy relationship is suggestive that the relative size of R^1-substituents directly influences isomerization of π-allyl intermediates. In this case, as the R^1-group becomes increasingly large C−C bond rotation of intermediate **E** is more 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,h,j,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 R^1-substituents relative to alkenyl nonaflate derivatives with larger substituents (i.e., 11:1 for R^1 = H, versus 3.1:1 for R^1 = *i*-Pr). The dependence of the regioselectivity on alkenyl nonaflate steric properties was supported by the

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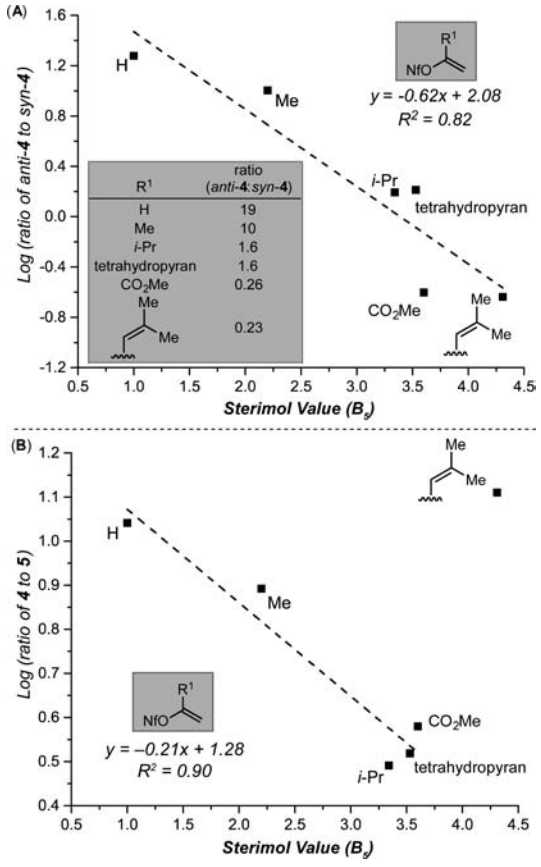

Figure 3. (A) Correlation between *anti* and *syn* 1,3-addition isomers and Sterimol B_5 values. (B) Correlation between 1,3- and 1,1-addition regioisomers and Sterimol B_5 values.

identification of a second free energy relationship between the logarithm of the regioselectivity and Sterimol B_5 values (Figure 3B).[13] This correlation is suggestive that the size of R^1-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-$(HO)C_6H_4$ (**4h**), 3-$(MeO_2S)C_6H_4$ (**4i**), and sterically encumbering 2-MeC_6H_4 (**4n**) substitution (Figure 4). Unfortunately, difunctionalization products with potentially reactive groups, including 4-$NO_2C_6H_4$ (**4k**) and 4-BrC_6H_4 (**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 R^2 = Ph (**4g**), versus 19:1 for R^2 = 4-$(NO_2)C_6H_4$ (**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 difunctionalization products in moderate to good product selectivity and yields.

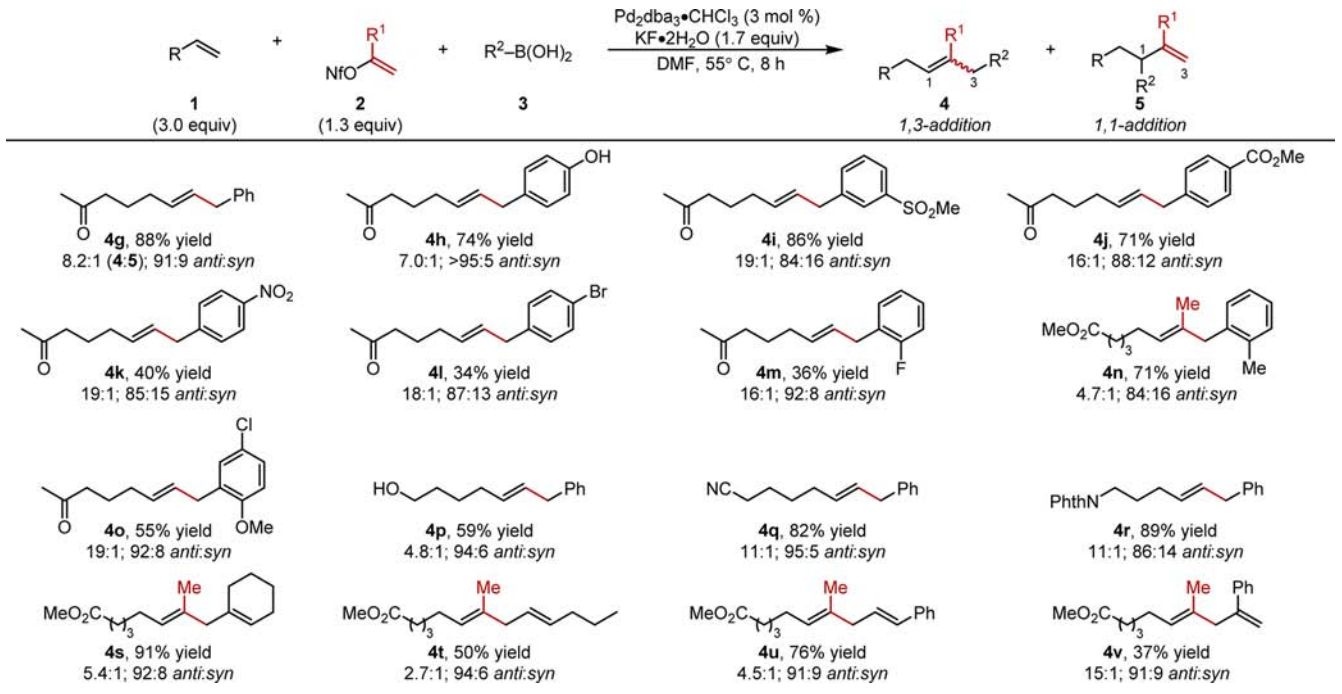

Figure 4. Exploration of the scope of the Pd-catalyzed 1,3-difunctionalization of terminal alkenes. Yields are reported as a combination of isomers of reactions performed on a 0.5 mmol scale. Structures of major stereoisomers are shown and were confirmed by NMR analysis. Isomeric ratios were determined by GC analysis of crude product mixture.

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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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00517.

Experimental procedures and full spectroscopic data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sigman@chem.utah.edu.

Notes

The authors declare no competing financial interest.

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(10) For complete optimization data, please refer to the Supporting Information.

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