Article

Pd-Catalyzed 1,3-Alkenylarylation of Skipped Diene via Metal Migration

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ABSTRACT: We disclose a palladium-catalyzed difunctionalization of skipped diene with alkenyl triflates and arylboronic acids to produce 1,3-alkenylarylated products. The reaction proceeded efficiently with Pd(acac)$_2$ as a catalyst and CsF as a base for a wide range of electron-deficient and electron-rich arylboronic acids as well as oxygen-heterocyclic, sterically hindered, and complex natural product-derived alkenyl triflates bearing various functional groups. The reaction produced 3-aryl-5-alkenylcyclohexene derivatives with 1,3-*syn*-disubstituted stereochemistry.

1,3-*syn*-disubstituted stereochemistry   18 examples; 41-70% yield
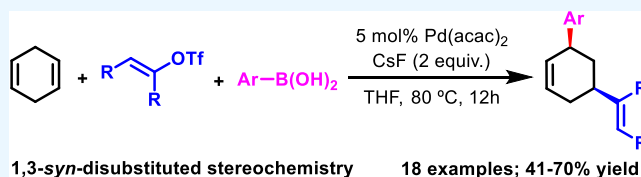
INTRODUCTION

Transition-metal catalyzed dicarbofunctionalization of unactivated alkenes is an emerging synthetic method that holds great promise to generate complex molecules rapidly from readily available starting materials.[1] In a classical approach, this process utilizes the potential of two reactive vicinal $C(sp^2)$ sites in alkenes to create two new carbon−carbon (C−C) bonds (Scheme 1A). This process is generally expected to proceed

Scheme 1. General Product Distribution during Alkene Difunctionalization
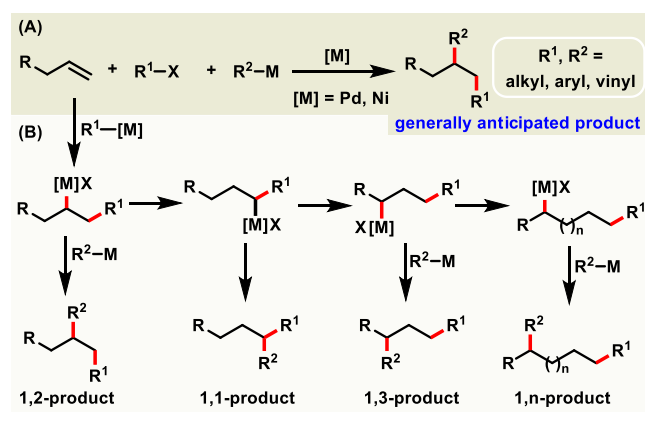
with the interception of alkylmetal intermediates (R-[M]) at the site of carbometalation to create the two C−C bonds adjacent to each other.

Since alkylmetal species are highly prone to undergo β-H elimination, products arising from metal migration via sequential β-H elimination and metal-hydride ([M]-H) insertion are also commonly observed during alkene dicarbofunctionalization reactions.[2] These metals in alkylmetal
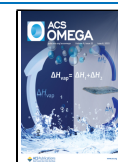
intermediates generally migrate to benzylic and allylic positions,[3] created in situ upon carbometalation by Ar/vinyl-[M] species, for thermodynamic stability when conjugated 1,3-dienes and unbiased alkenes are utilized as alkene sources generating products with 1,1- and 1,n-difunctionalization (Scheme 1B).[3i,q,4] Recently, we[5] and Zhao[6] reported a coordination-assisted Ni-catalyzed 1,3-dicarbofunctionalization reactions of alkenes with ArX and ArZnX/ArB(OH)$_2$. In this process, an initial, transiently generated six-membered nickellacycle underwent coordination-assisted ring contraction to a five-membered nickellacycle for thermodynamic stability via β-H elimination/[M]-H insertion facilitated by the strong coordination of imine and pyrimidine.

Unlike conjugated 1,3-dienes, skipped (1,4) dienes furnish products arising from 1,3-difunctionalization owing to the propensity of the metal to migrate to the allylic position of the additional alkene (Scheme 2). However, this process has mainly been successful for the generation of a combination of a C−C bond with C−N, C−B, C−O, C−Cl, and C−F bonds (Scheme 2a).[3a,d,7] The generation of two 1,3-C−C bonds in skipped dienes is limited to an intramolecular process in which an alkyl-Pd(II) intermediate, generated upon cyclization of aryl iodide on to a tethered skipped diene, is intercepted by a malonate nucleophile (Scheme 2b).[8] Recently, Yin and co-workers also reported 1,3-diarylation of 1,4-cyclohexadiene.[9] Herein, we report a three-component dicarbofunctionalization
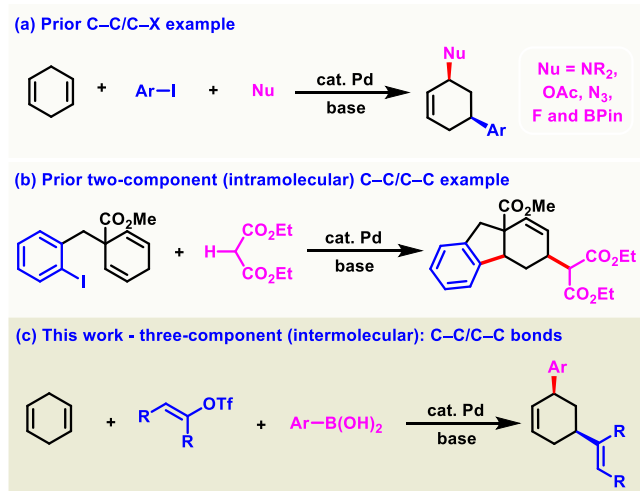
Scheme 2. General Product Distribution during Alkene Difunctionalization

(a) Prior C–C/C–X example

(b) Prior two-component (intramolecular) C–C/C–C example

(c) This work - three-component (intermolecular): C–C/C–C bonds

of a skipped diene with alkenyl triflates and arylboronic acids that creates two C–C bonds at 1,3-positions (Scheme 2c).

■ RESULTS AND DISCUSSION

In our initial studies, we examined various organometallic reagents as a source of carbon nucleophile in combination with alkenyl triflates as electrophiles in the presence of Pd catalysts (see the Supporting Information for details). While phenylmagnesium, phenylzinc, and phenylsilicon reagents did not provide any product (Table 1, entry 1), we were pleased to discover that phenylboronic acid provided the alkenylarylated product **1** in 70% yield in the presence of 5 mol % Pd(acac)$_2$ and 2 equiv of CsF (entry 2).[10] The regio- and stereochemistry of product **1** was confirmed by two-dimensional (2D) homonuclear (COSY) and heteronuclear (HSQC) NMRs.

The reaction furnished no product without CsF or in the presence of NaOAc (entries 3 and 4), suggesting that the reaction proceeded by fluoride-promoted transmetallation.[11] Decreasing the equivalence of either 1,4-cyclohexadiene or increasing cyclohexenyl triflate lowered the product yield (entries 5–6), suggesting that the appropriate concentration of each reagent is essential for high product yield.[12] Other Pd catalysts, such as Pd$_2$(dba)$_3$ and Pd(PPh$_3$)$_4$, generated the product in low yield (entries 7 and 8). Pd and Ni catalysts lacking any ancillary ligands, like Pd(OAc)$_2$ and NiBr$_2$, did not form any product (entries 9 and 10). While *N*-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), and MeCN furnished the product in low yields (entry 11), the reaction could be conducted in dioxane, dimethylformamide (DMF), or toluene, which generated the product in moderate yields (entry 12).

With the optimized conditions in hand, we explored the scope of the alkenylarylation reaction with regard to both arylboronic acids and alkenyl triflates (Table 2). Examination of the various arylboronic acids indicated that the reaction well tolerated both electron-deficient and electron-donating substituents generating the alkenylarylated products in good yields (**2–14**). The reaction was compatible with substituents, such as methyl, 1,3-dimethyl, methoxy, and ester (**8–14**). The reaction also remained successful with both cyclic (**2–14**) and linear alkenyl triflates (**15**). Additionally, we found that the reaction was tolerant of oxygen heterocycles. For example, the reaction was compatible with oxygen-containing heterocyclic triflate (**4**) and triflates containing cyclic acetal (**5** and **14**) and OTBS (**6**) in addition to the methyl substituent (**7–8**). We also examined alkenyl trilates derived from more sterically hindered natural products, such as camphor, and complex structure like cholestenone, which also furnished alkenylarylated products (**16–18**) in good yields. These examples demonstrate that the current Pd-catalyzed alkenylarylation

Table 1. Optimization for 1,3-Alkenylarylation[a]
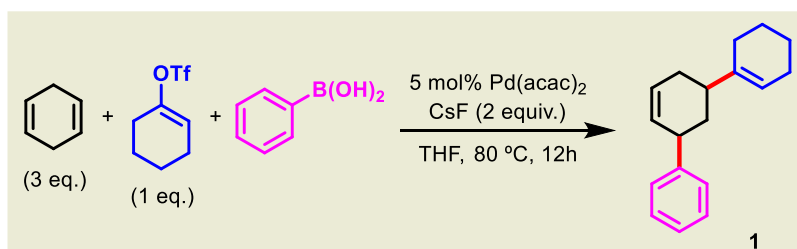
entry	deviation in reaction conditions	yields of **1**[b] (%)
1	PhMgCl, PhZnI or PhSi(OMe)$_2$ instead of PhB(OH)$_2$	0
2	no change	70
3	no CsF	2
4	NaOAc instead of CsF	0
5	1 equiv cyclohexadiene	42
6	2 equiv of triflate	44
7	10% Pd$_2$dba$_3$ instead of Pd(acac)$_2$	24
8	Pd(PPh$_3$)$_4$ instead of Pd(acac)$_2$	3
9	Pd(OAc)$_2$ instead of Pd(acac)$_2$	0
10	NiBr$_2$ instead of Pd(acac)$_2$	0
11	NMP, DMSO, or MeCN instead of THF	3–24
12	dioxane, DMF, or toluene instead of THF	37–47

[a]Reaction conditions: diene (0.3 mmol), vinyl triflate (0.1 mmol), boronic acid (0.1 mmol), and tetrahydrofuran (THF) (0.5 mL). [b]Yields determined by ^{1}H NMR using pyrene as an internal standard.
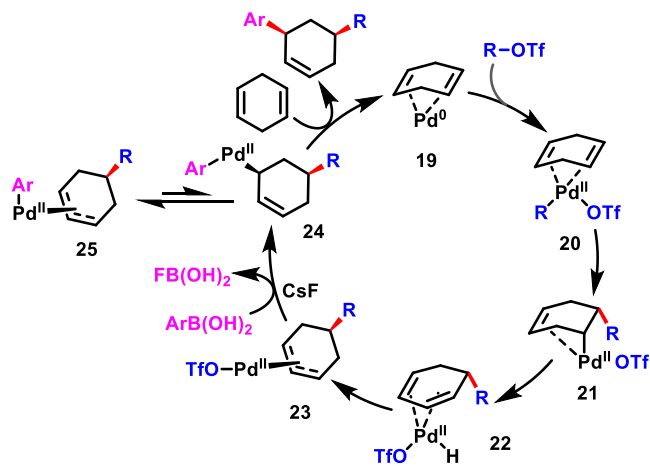
Table 2. Scope of 1,3-Vinylarylation-1,4-cyclohexadiene[a,b]
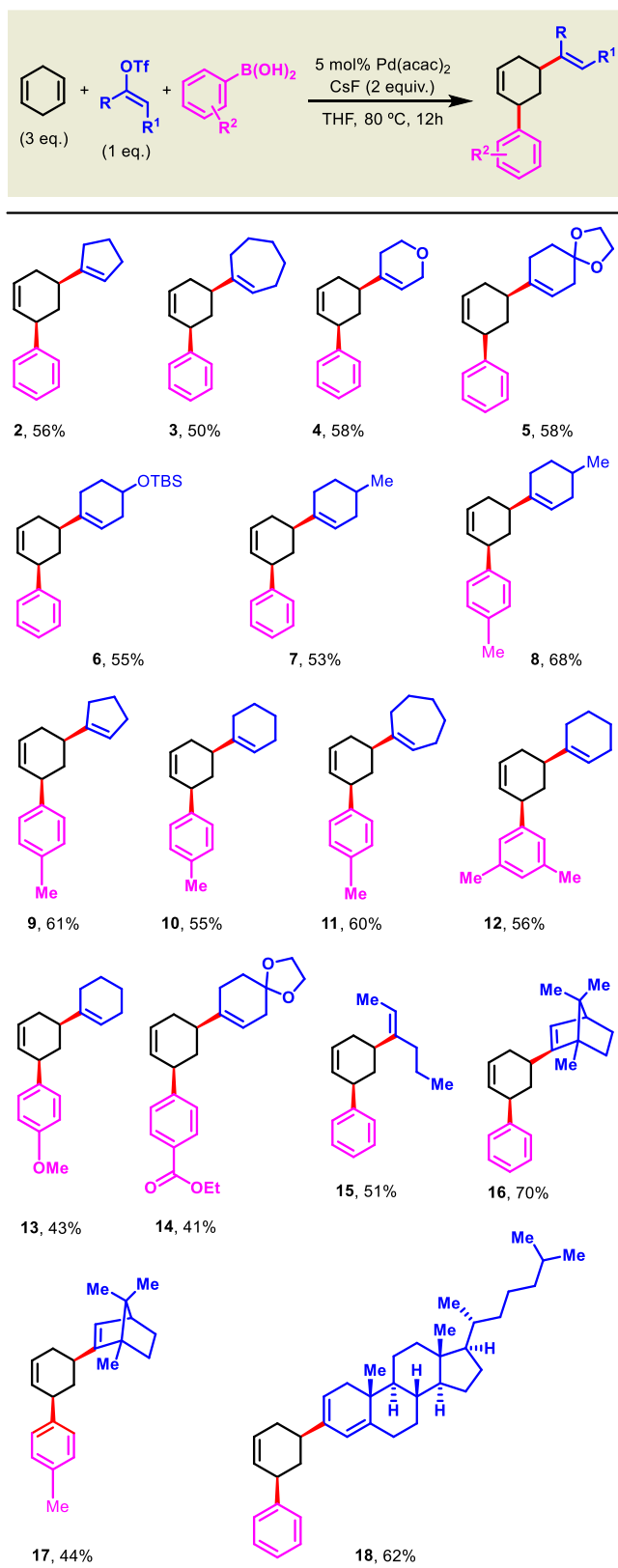
reaction could be applied to elaborate both simple and complex natural products.

Based on literature reports[8] and regiochemical and stereochemical outcomes of the current reaction, we propose a catalytic cycle (Scheme 3). The reaction is initiated by diene-

Scheme 3. Proposed Catalytic Cycle

bound Pd(0) (**19**), followed by oxidative addition of alkenyl triflate to form an alkyl-Pd(II) intermediate (**20**). The alkyl-Pd(II) species then undergoes sequential β-H elimination (**21**) and Pd(II)-H reinsertion into the resultant Pd-bound 1,3-diene (**22**) to generate a π-allyl-Pd(II) intermediate (**23**). The 1,3-*syn*-stereochemistry of the products in Table 2 suggests that Pd(II)-H remains bound to the in situ-generated 1,3-diene upon *syn*-migratory insertion of the Pd(II)-H species creating a π-allyl-Pd(II) intermediate (**23**) with a *syn*-stereochemical relationship between the alkenyl component derived from alkenyl triflates and the Pd(II)-OTf moiety in species **23**. Subsequent transmetalation with ArB(OH)$_2$, followed by the stereoretentive C−C bond-forming reductive elimination from an alkyl(aryl)-Pd(II) intermediate (**24**) generates the 1,3-*syn*-alkenylarylation products and regenerate the Pd(0) catalyst **19**.

■ CONCLUSIONS

Overall, we have successfully demonstrated a new method of preforming a completely diastereoselective 1,3-alkenylarylation reaction of skipped diene with alkenyl triflates and arylboronic acids using Pd(dba)$_2$ as a catalyst in the presence of CsF as a base. This method was achieved through metal migration ensuing via sequential β-H elimination and Pd(II)-H reinsertion of an alkylpalladium(II) intermediate, a process that proceeds by a stereoretentive process generating products with two new substituents in *syn*-geometry. The new method is applicable to a variety of cyclic and acyclic alkenyl triflates and arylboronic acids. The reaction also tolerates a range of functional groups, including esters, OTBS, cyclic acetals, and oxygen heterocycles, and can be applied to sterically bulky and complex natural products.

■ EXPERIMENTAL SECTION

General Information. All of the glassware dried in an oven before use. All chemicals were obtained from commercial sources and used as received. Corresponding ketones for alkenyl triflates were synthesized according to literature procedures.[13] NMR spectra obtained for new compounds

[a]Reaction conditions: diene (1.5 mmol), vinyl triflate (0.5 mmol), boronic acid (0.5 mmol), THF (0.5 mL). [b]Isolated yields are reported.

were recorded at the NMR Facilities in the Department of Chemistry at the Penn State University. NMR spectra were recorded on a Bruker instrument spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) at room temperature. Chemical shifts are recorded in parts per million. ^{1}H NMR shifts are referenced to chloroform-d (d = 7.26), and ^{13}C shifts are referenced to chloroform-d (d = 77). NMR splitting patterns were represented by the following: s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. High-resolution mass spectra for new compounds were recorded at the Mass Spectrometry Facility at the University of Texas Austin.

General Procedure for Reaction Screening. On the bench outside in air, $Pd(acac)_2$ (1.5 mg, 0.005 mmol, 5 mol %), phenylboronic acid (12.2 mg, 0.1 mmol), cesium fluoride (30.4 mg, 0.2 mmol), cyclohex-1-en-1-yl trifluoromethanesulfonate (20.3 mg, 0.1 mmol), and 1,4-cyclohexadiene (24.4 mg, 0.3 mmol) were added to a 1 dram vial with a stir bar. The mixture was then dissolved in 0.5 mL of THF. The vial was capped tightly and placed on a hot plate that was preheated to 80 °C and stirred vigorously for 12 h. After 12 h, the reaction mixture was cooled to room temperature. In the reaction mixture, 50 μL of pyrene (0.010 mmol, 0.20 M stock solution) was added as an internal standard. Water was then added with ethyl acetate and an organic wash was performed 3 times where the organic layer was removed. The reaction was then filtered through a silica pad (pipette column), and the solvent was removed in a rotary evaporator. The residue was dissolved in $CDCl_3$, and an NMR spectrum was acquired. The yield was determined by integrating a product peak at 3.5 ppm against the pyrene peak at 8.06 ppm.

■ ASSOCIATED CONTENT

⑤Ⓘ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01839.

> Experimental procedures and characterization data for all compounds and copies of NMR spectra of all of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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