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A Palladium-Catalyzed Three-Component Cross-Coupling of Conjugated Dienes or Terminal Alkenes with Vinyl Triflates and Boronic Acids

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Abstract

A three-component coupling of vinyl triflates and boronic acids to alkenes catalyzed by palladium is reported. Using 1,3-dienes, selective 1,2-alkene difunctionalization is observed, whereas the use of terminal alkenes results in 1,1-alkene difunctionalization. The reaction outcome is attributed to the formation of stabilized, cationic Pd-π-allyl intermediates to regulate β-hydride elimination.

Significant effort has been afforded to the development of high utility methods involving palladium-catalyzed alkene functionalization as highlighted by the Heck reaction[1] and the Wacker oxidation.[2] Inspired by the key mechanistic motifs of these fundamental reactions, a focus of our research program over the last several years has been the advancement of palladium-catalyzed alkene difunctionalization reactions with the ultimate goal of selectively introducing two groups across the alkene.[3–7] As a specific example, we have reported the diarylation[4c,4d,6,7] of conjugated and terminal alkenes using oxidative palladium catalysis (Scheme 1a). In this reaction, two aryl groups originating from an arylstannane are added across a 1,3-diene (or styrene) to yield the 1,2-diarylation product. Mechanistically, this reaction is thought to initiate by transmetallation to form Pd-aryl species **A**, Heck insertion of a conjugated diene yields **B**, followed by stabilization of the Pd-alkyl as a π-allyl **C**. Subsequent cross coupling of a second equivalent of an aryl stannane results in product formation.[4d] The success of this reaction is partially attributed to stabilization of the electrophilic Pd-species by formation of either a π-allyl (for dienes)[8] or a π-benzyl (for styrenes)[4c,4d,9] intermediate suppressing β-hydride elimination. The obvious synthetic limitation of this 1,2-alkene difunctionalization reaction is the introduction of two identical aryl groups from the arylstannane as well as reasonably complex reaction conditions.[4d]

To overcome this significant synthetic drawback, we considered an alternative and perhaps simpler approach. Specifically, the use of Pd(0) initiated catalysis is proposed wherein a vinyl triflate undergoes oxidative addition to yield Pdvinyl species **D**. Heck insertion of a diene should produce intermediate **B'** which is closely related to the proposed intermediate in the oxidative Pd-catalyzed diarylation reaction and should be stabilized by formation of a π-allyl **C'** to suppress β-hydride elimination. It should be noted that vinyl triflates were specifically selected to initiate the catalysis since highly electrophilic Pd-species should result in alkene insertion in preference to the more common Suzuki coupling sequence.[10] To complete the process, transmetallation of a boronic acid derivative and reductive elimination

will introduce two *different* groups into the alkene framework to yield skipped diene products.[11]

Reports of related three-component coupling reactions of this type with Pd have been generally limited to substrates that are unable to undergo β-hydride elimination after Heck insertion such as norbornenes,[12] alkynes,[13] and carbene precursors.[14] Allenes as the "alkene" coupling partner have been reported, where a Pd-π-allyl species is directly formed via migratory insertion to presumably avoid β-hydride elimination in a manner similar to our proposal.[15] Herein, we present the successful development of a three-component coupling[16] to achieve the formation of two sp^2–sp^3 carbon-carbon bonds from the alkene framework using vinyl triflates as the organic electrophile and boronic acids as the organometallic reagent. Surprisingly, this complexity generating reaction occurs under very simple and mild reaction conditions, where alkene 1,2-difunctionalization is achieved using conjugated dienes. Extension to more challenging terminal alkenes, which has not previously been reported, is also presented, yielding the 1,1-alkene difunctionalization products under identical reaction conditions.

For optimization, vinyl triflate **1a**, diene **2a** and boronic acid **3a** were selected (Table 1). Gratifyingly, the optimized conditions are simple, in which catalytic amounts of $Pd_2(dba)_3$ in the presence of stoichiometric KF as base in dimethylacetamide (DMA) as solvent are required for selective formation of the three-component coupling product **4a**. Other bases, such as K_2CO_3, Cs_2CO_3, and K_3PO_4 also gave the desired product in similar yields and the addition of exogenous water does not impact the overall outcome of this reaction (see supporting information). No added ligand is necessary, implicating to us the importance of solvent acting as a ligand on Pd.[17] Exploration of other solvents highlights this point revealing that common amide solvents (entries 4 and 5) lead to better selectivity for **4a** than other polar solvents such as *tert*-amyl alcohol (entry 2) and DMSO (entry 3) wherein both Heck and Suzuki products are formed in substantial amounts. Addition of several monodentate phosphine ligands (entries 6 and 7) also leads to mixtures of products. Of note, the use of tricyclohexylphosphine promotes the Heck reaction while also forming the diene hydroarylation product, presumably from a Pd-hydride formed in the reaction.[8i] The reaction temperature modestly affects the reaction outcome (entries 8 and 9), while the use of either boronic esters (entry 10) or trifluoroborates (entry 11) leads to lower yields of **4a**. A 1:1 ratio of alkene and vinyl triflate is required to achieve excellent yields of the desired skipped diene products with only a modest excess of the boronic acid.

Using the standard conditions, we explored the scope of the three-component coupling of 1,3-dienes (Table 2). Previous results from our lab suggested that selective 1,2-addition reactions in the cross-coupling of π-allyl intermediates **C** is achieved by using aryl 1,3-dienes.[8i] Therefore, both electron-rich and electron-deficient aryl-substituted dienes were evaluated, yielding the corresponding three-component coupling products in good to excellent yields with >95:5 selectivity for the 1,2-addition product. A variety of vinyl triflates in combination with aryl boronic acid derivatives with common functional groups were evaluated. The use of simple cyclic vinyl triflates with different ring sizes (**4a, 4d, 4f, 4g**, and **4l**) led to excellent yields. Heterocyclic vinyl triflates (**4b, 4h** and **4i**) also provides the corresponding products in modest to excellent yields. An acyclic vinyl triflate (**4j**) gave the desired product in moderate yield. Using a vinyl triflate derived from (+)-camphor produces **4k** in high yield but unfortunately a nearly 1:1 mixture of diastereomers. Various aryl boronic acids were also explored, wherein electronically disparate substituents or *ortho*-substitution on the arene had little influence on the reaction outcome. Of note, aryltriflates are not effective coupling partners and styrenes lead to a mixture of constitutional isomers under these reaction conditions.

The formation of a π-allyl-Pd-species similar to **C'** is a key proposal in this process as depicted in Scheme 1c. To probe if a species of this type is undergoing β-hydride elimination during the reaction, deuterated substrate **d$_2$-2a** was synthesized and subjected to the standard reaction conditions. No deuterium migration occurs during the course of the reaction as determined by ^{1}H-NMR, ruling out the occurrence of β-hydride elimination of the π-allyl-Pd (Scheme 2a). This suggests as hypothesized above that π-allyl-Pd formation controls the outcome of the reaction, which is in good agreement with our previous observation in the 1,1-oxidative diarylation of terminal olefins with organostannanes that a deuterium label migrates in order to form a stabilized π-benzyl-Pd intermediate (Scheme 2b).[4c,4d] The combination of these experiments suggests that the use of a terminal olefin in the current three-component coupling protocol should yield the 1,1-alkene difunctionalization product. Mechanistically, Heck insertion of a terminal olefin after oxidative addition of a vinyl triflate would yield unstabilized Pd-alkyl intermediate **B"**. Selective β-hydride elimination at the ayllic site and reinsertion of the Pd-hydride results in the formation of π-allyl-Pd intermediate **C"**. Subsequent transmetallation of a boronic acid and reductive elimination produces the desired three-component coupling product. It should be noted that the use of simple terminal alkenes in three-component coupling chemistry of this sort has not been reported to the best of our knowledge.

With no change to the optimized reaction conditions, the three-component coupling of terminal alkenes leads to generally excellent selectivity and yields for the desired 1,1-alkene difunctionalization product (Table 3). Olefins bearing common functional groups such as a nitrile (**8e**), a primary alkyl chloride (**8g**), esters (**8j**, **8k**), a protected amine (**8l**), a free primary alcohol (**8f**) and a primary bromide (**8h**) were found to be compatible under these reaction conditions. Unfortunately, unprotected carboxylic acids and basic amines did not successfully undergo the three-component coupling. A variety of arylboronic acids proved to be effective coupling partners, providing high yields regardless of their electronic nature. A homoallylic alcohol cleanly undergoes coupling, although a 1:1 mixture of diastereomers results (**8m**). As noted above, heterocyclic vinyl triflates are excellent partners in this reaction (**8c**, **8d**, **8l**). In contrast to conjugated dienes, a limitation of this method is a general requirement of six-membered cyclic vinyl triflates to achieve selective formation of the endocyclic double bond (five and seven-membered ring vinyl triflates yield a mixture of constitutional isomers). As an example, coupling with an acyclic vinyl triflate produced a 1:1 mixture of two regioisomers **8n** and **8n'** (Scheme 3). These results further indicate the formation of a π-allyl-Pd intermediate like **C"**. Presumably, in the case of six-membered vinyl triflates, the thermodynamically more favorable endocyclic double bond is formed. Control of constitutional isomer formation should considerably expand the utility of this process and is under current investigation.

In summary, we have combined the Suzuki reaction and the Heck reaction in an intermolecular fashion to achieve the difunctionalization of 1,3-dienes and terminal alkenes. The conditions are quite simple using reagents that are readily accessed and are not required in extreme excess. The scope of this reaction is relatively broad in terms of functional group compatibility and the products formed would be difficult to prepare rapidly using current methods. The success of this reaction class is attributed to the formation of stabilized, cationic π-allyl-Pd intermediates. In the case of conjugated dienes, the π-allyl-Pd intermediate is formed initially from Heck insertion of the alkene, which is faster than Suzuki cross-coupling under the optimized reaction conditions. In contrast, terminal alkenes undergo π-allyl-Pd formation by a proposed β-hydride elimination/Pd-hydride reinsertion rearrangement. Additionally, the ability to form sp^2–sp^3 carbon-carbon bonds on the alkene framework with *different* coupling partners holds significant promise for synthetic endeavors. Future work is focused on probing the synthetic applications of this reaction

class by developing enantioselective variants, evaluating broad classes of coupling partners, and understanding the underlying mechanistic features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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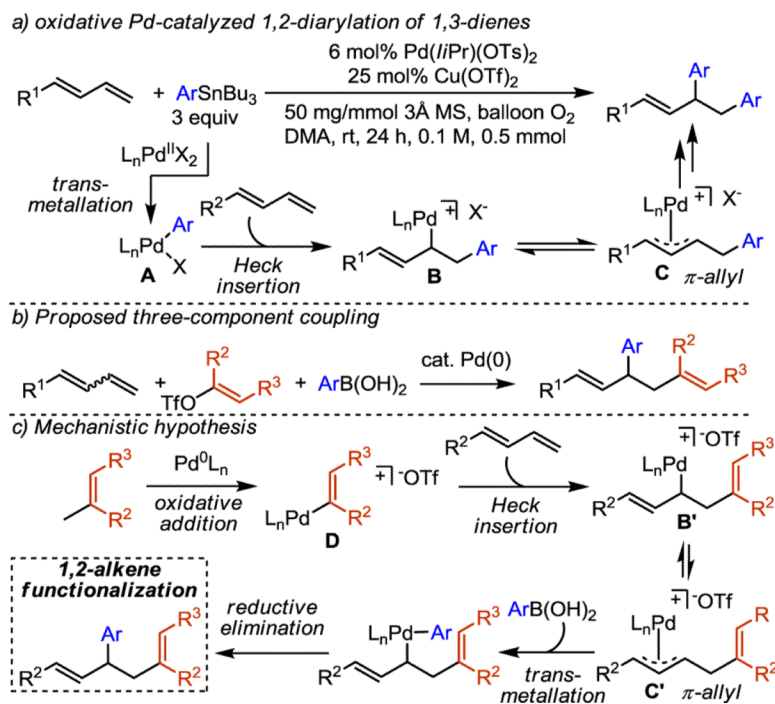
Scheme 1.
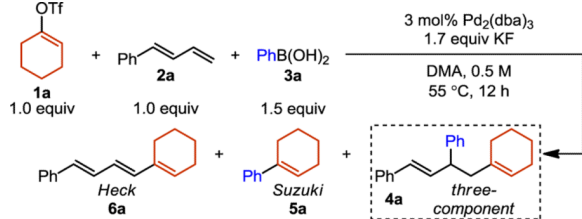Proposed three-component coupling of conjugated dienes with vinyl triflates and aryl boronic acids.
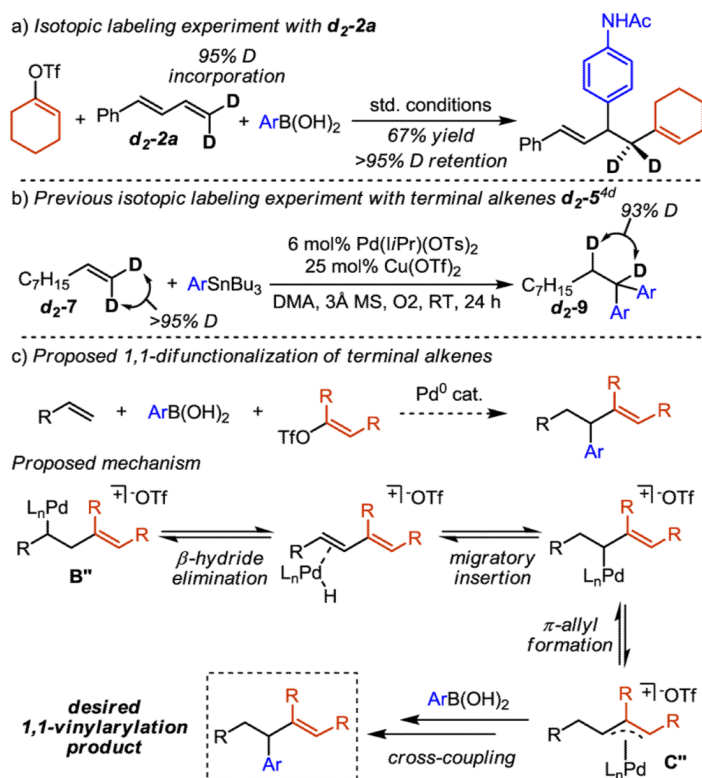
Scheme 2.
Mechanistic analysis.

Scheme 3.
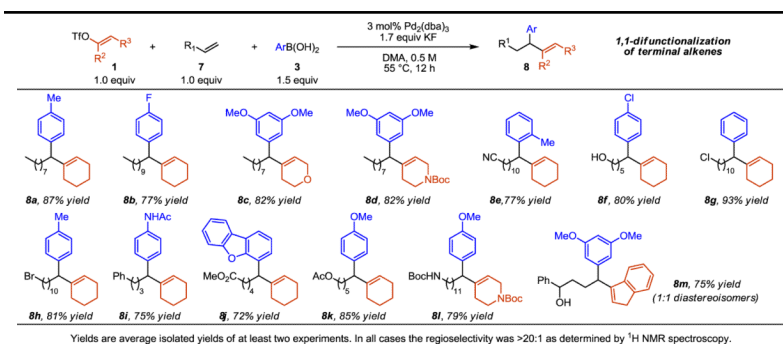Three-component coupling of an acyclic vinyltriflate.

Table 1

Initial evaluation of the three-component coupling of **1a, 2a** and **3a** to form **4a**.

Entry	Changes	% Conv.[a]	%4a[b]	4a : 5a : 6a
1	standard conditions	100	90	> 99% of **4a**
2	^{t}AmylOH (solvent)	63	29	71 : 3 : 26
3	DMSO (solvent)	95	21	20 : 10 : 70
4	NMP (solvent)	100	78	> 99% of **4a**
5	DMF (solvent)	100	85	> 99% of **4a**
6	7 mol% P(o-tol)$_3$	50	14	17 : 67 : 17
7[c]	7 mol% P(Cy)$_3$	100	10	20 : <1 : 80
8	R.T.	99	53	90 : 7 : 3
9	80 °C	98	77	93 : 5 : 2
10[d]		100	40	33 : <1 : 67
11[e]	PhBF$_3$K	20	10	75 : <1 : 25

[a]Conversion of **2a**, measured by GC using an Internal standard.

[b]GC yield using an internal standard.

[c]Hydroarylation product (*E*)-but-1-ene-1,3-dlyldlbenzene was found in 50% GC yield.

[d]3.0 equiv of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane was added instead of PhB(OH)$_2$.

[e]3.0 equiv of PhBF$_3$K was added instead of PhB(OH)$_2$.

Table 2

Scope of the three-component coupling of vinyl triflates, aryl boronic acids, and conjugated dienes.[a]

Table 3

Scope of the three-component coupling of vinyl triflates, aryl boronic acids and terminal alkenes.[a]