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Synthesis of Functionalized 1,3-Butadienes via Pd-Catalyzed Cross-Couplings of Substituted Allenic Esters in Water at Room Temperature

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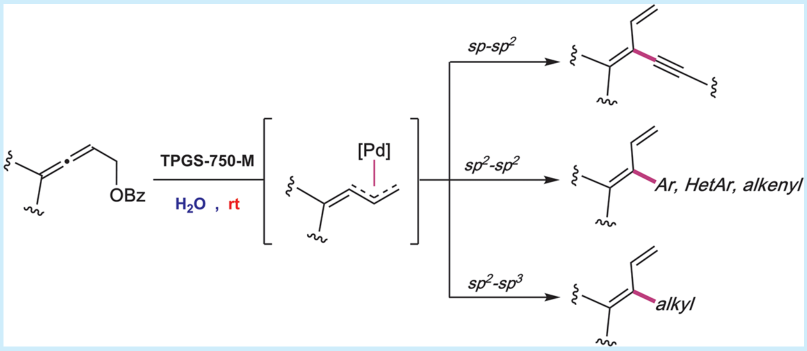
Supporting Information



ABSTRACT: An environmentally responsible, mild method for the synthesis of functionalized 1,3-butadienes is presented. It utilizes allenic esters of varying substitution patterns, as well as a wide range of boron-based nucleophiles under palladium catalysis, generating sp−sp^2, sp^2−sp^2, and sp^2−sp^3 bonds. Functional group tolerance measured via robustness screening, along with room temperature and aqueous reaction conditions highlight the methodology's breadth and potential utility in synthesis.

Historically, 1,3-butadienes have been relied upon in target-oriented syntheses as chemical pillars for generating molecular complexity. Uses of this motif include epoxidations, regioselective conjugate additions, borylations, and, in particular, [4 + 2] Diels−Alder reactions, with the latter being strong testimony, in and of itself, regarding their worth in synthesis.[1] Traditional inroads to 1,3-butadienes rely upon (1) elimination reactions, (2) reduction or isomerization of enynes, (3) enyne metathesis, (4) Wittig/HEW-type olefinations of conjugated carbonyl compounds, and (5) cross-coupling of alkenyl electrophiles and organometallics. These usually take place in organic solvents and may require elevated temperatures and/or inert atmosphere conditions. High catalyst loadings are often accompanied by a narrow or specific substrate scope and can lead to undesired side reactions characteristic of alternative modes of catalysis. Hence, advances in these approaches, especially from a green chemistry perspective, for acquiring this time-honored functionality remain desirable.[2]

Herein, we report on palladium-catalyzed formation of functionalized 1,3-butadienes via cross-couplings of substituted allenic esters with boron and acetylenic nucleophiles under aqueous micellar catalysis conditions. This approach provides both new and more efficient disconnections leading to streamlined syntheses based on ready access to these key structural units.

Previously, we demonstrated that allylic ethers are competent reaction partners in Suzuki−Miyaura cross-couplings under micellar catalysis.[3] Use of an analogous allenic electrophile was considered as an alternative coupling partner with a suitable boron nucleophile under related conditions. Upon product isolation it became apparent that, with allenyl systems, coupling occurred exclusively at the central allenic carbon generating 2-substituted 1,3-butadienes as the sole product (Scheme 1).[4] By contrast, use of iridium in related displacements of α-aryl substituted allenic esters by alkylzinc reagents leads exclusively to allenic products of "outer-sphere"-type substitution.[5]

Although this Pd-catalyzed transformation had been briefly disclosed, it was envisioned that an in-depth study could further broaden the scope of this route to important conjugated dienes, while further documenting its use under environmentally responsible conditions.[6] Our initial exploration of related conditions allowed specifically for the construction of symmetrical and mixed [3]−[6]dendralenes,[7] which we disclosed in anticipation of a more detailed investigation leading exclusively to the 1,3-butadiene array that now forms the basis of this report.

Further catalyst screening revealed that surprisingly, all palladium catalysts surveyed promoted the desired trans-

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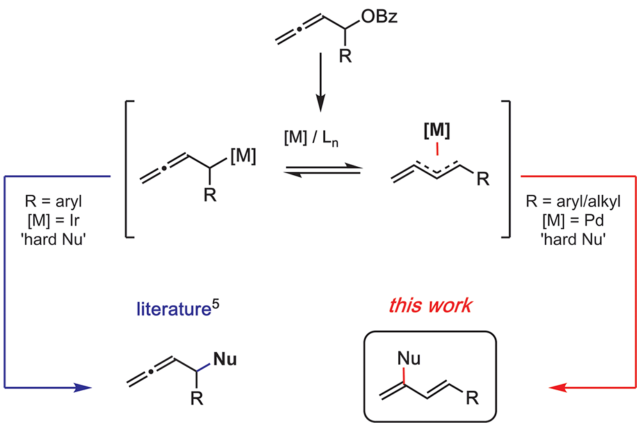
Scheme 1. Orthogonal Metal Activation and Substitution of Allenyl Electrophiles with “Hard” Nucleophiles

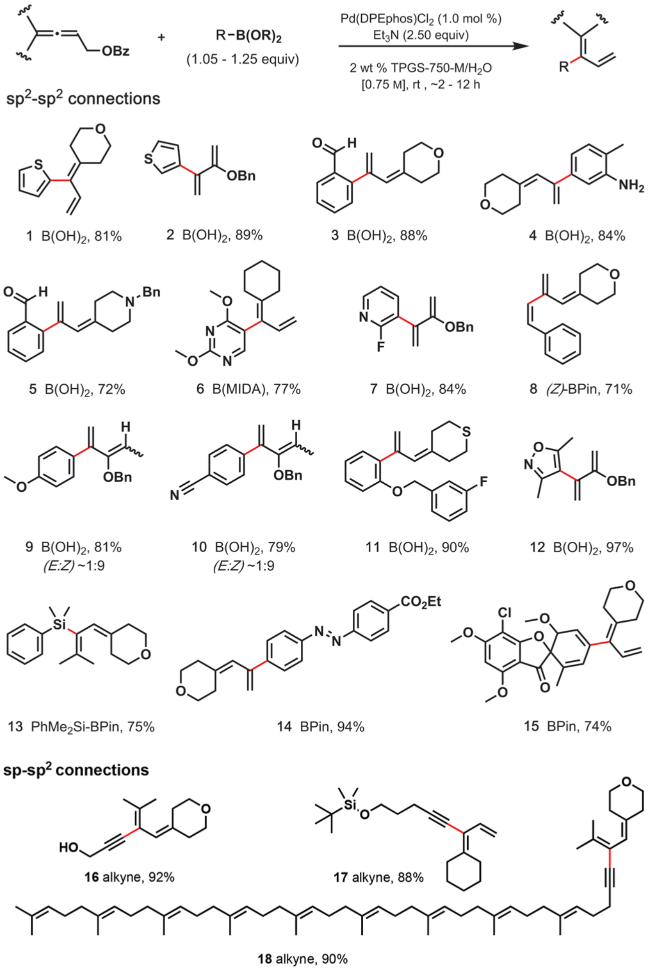


formation. Differences were mainly regarding the time required for full conversion, ranging from 2 min (e.g., with $\leq$1.0 mol % Pd(DPEphos)Cl$_2$) to 4 h (using 5.0 mol % of 10 wt % Pd/C) for the model system (phenylboronic acid + cyclohexyl allenic ester, not shown). Use of other transition metal catalysts (e.g., Ni(II), Rh(I), Rh(III)) resulted in no consumption of the allenic ester. Although less than an equivalent of base (Et$_3$N) could be employed, for particularly highly crystalline boron derivatives, it was found that use of 2.50 equiv was generally sufficient across a wide range of coupling partners. As many of the initial products prepared were of low polarity, separation from protodeborylated materials was occasionally problematic. Fortunately, running the reactions with 1.00−1.05 equiv of boron reagent led to an improved impurity profile without adversely affecting isolated yields.

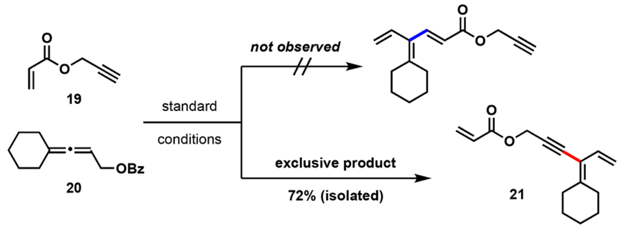
With the general conditions established (see Scheme 2, top), a range of arylboronic acids, as well as B(MIDA) and BPin derivatives, were tested as coupling partners on an array of allenic esters bearing varying substitution patterns. Aryl rings containing *ortho*-, *meta*-, and *para*-substituents were well tolerated independent of their electron-donating or -withdrawing nature. Gratifyingly, these reactions were not limited to simple aryl boron derivatives, as heteroaromatic products (**1**, **2**, **6**, **7**, and **12**) and acetylenic products (**16**, **17**, and **18**) were easily formed. Use of Suginome’s PhMe$_2$Si-BPin smoothly led to butadienylsilane **13**. An azobenzene also participated, readily giving rise to **14**, an operationally simple procedure for producing bathochromic shifted photoactive materials potentially of use in materials chemistry, organo-photovoltaics, and photopharmacology.[8] Of note is the ability to couple a stereodefined (Z)-vinylboronate with complete retention of the initially observed geometry (see **8**, a stereodefined [3]dendralene). Moreover, use of the antifungal derivative of griseofulvin (W.H.O. list of essential medicines)[9] led to the rapid construction of a potentially biologically active [4]-dendralene derivative **15** containing a functionality suitable for further manipulation.

The initial use of C$_{sp}$−BF$_3$K salts[10] smoothly furnished the corresponding 2-alkynyl-1,3-butadiene derivatives. However, it became apparent upon exploring the reactivity of acrylate **19** toward **20** that not only was the use of an acetylenic boron precursor not required to effect a Sonogashira-type cross-coupling, but also that the nucleophilicity of terminal alkynes, relative to a competitive Heck-type pathway, was significantly higher under micellar catalysis conditions (Scheme 2, bottom, and Scheme 3).

Scheme 2. Representative Scope of sp^2−sp^2 and sp−sp^2 Bond Formations



Scheme 3. Observation of Preferential Sonogashira vs Heck Coupling

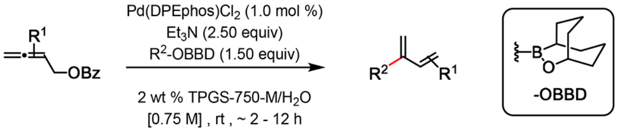


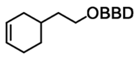
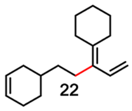
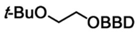
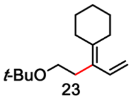
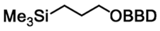
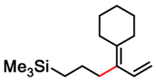
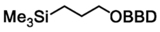
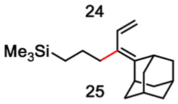
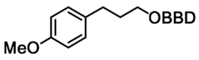
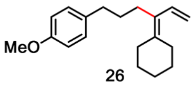
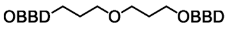
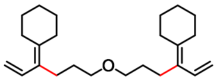
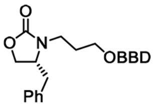
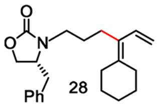
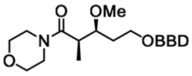
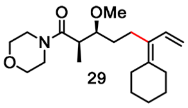
While establishing substrate scope, attempts employing alkyl (sp^3) boron nucleophiles led to mixed results. The use of various boron species such as acids, pinacol esters, MIDA boronates, and BF$_3$K salts all failed to generate the desired products. While Suzuki has shown that 9-BBN derivatives could be employed,[6a] their pyrophoric nature, low stability, and limited shelf life made them unattractive reagents for our methodology. We reasoned that the use of borinate derivatives as an intermediary between boronic acids and boranes might provide sufficient reagent stability and safety, with adequate electrophilicity to eventually lead to a two-electron transmetalation.[11a] Soderquist and coworkers have shown previously that selective mono-oxidation of

9-BBN derivatives with TMANO (trimethylamine *N*-oxide) leads to more robust boron species (R-OBBD, *B*-alkyl-9-oxa-10-borabicyclo[3.3.2]decane) with improved air stability.[11b] Indeed, these −OBBD reagents promoted the construction of this difficult C−C bond, due to their higher reactivity compared to boronic acids, as well as their increased stability relative to the corresponding 9-BBN derivatives, in an open-to-air, aqueous system.[11c]

As shown in Table 1, a broad range of sp^3 groups bearing useful synthetic functionalities all provided the corresponding dienes in modest to excellent yields with minimal side product formation. The yields of entries 1−3 are diminished presumably due to high product volatility. A heavier allenic ester displayed no such problems in this regard (compare entries 3 and 4). A *bis*-nucleophile promoted a double sp^2−sp^3 cross-coupling producing bis-diene adduct **27** in a single operation (entry 6). Likewise, nucleophiles possessing chirality such as oxazolidinone (entry 7) and an aldol adduct (entry 8) were cleanly coupled under these conditions with no observable erosion in dr,[12] demonstrating the potential utility of this method in complex molecule synthesis.

Table 1. Representative Examples of sp^2−sp^3 Bond Formations via −OBBD Derivatives

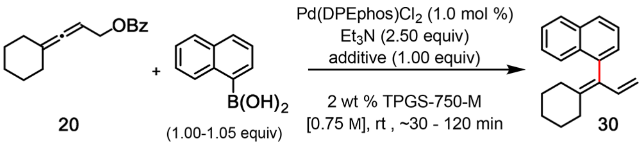


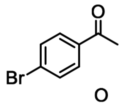
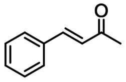
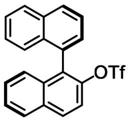
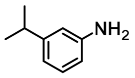
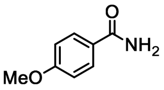
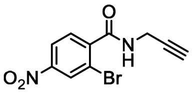
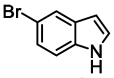
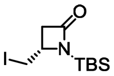
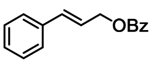
entry	educt	1,3-diene product	isolated yield (%)
1		 **22**	54
2		 **23**	64 (48 h)
3		 **24**	65
4		 **25**	87
5		 **26**	94
6		 **27**	43
7	*(R)* - *(+)* 	 **28**	93
8		 **29**	77

With a broad spectrum of successfully coupled reagents of synthetic utility in hand, an investigation was made so as to examine functional group compatibility. This was carried out based on Glorious' robustness screen as a method of establishing functional group tolerance. This has emerged as a powerful tool to quickly and accurately predict the compatibility of larger and structurally more diverse coupling partners (i.e., natural products) without having to engage precious and/or multistep processes to prepare substrates for initial screenings.[13]

Allenic ester **20** was used initially in the absence of an additive to establish a baseline measure of reaction efficiency leading to diene **30** (Table 2, entry 1). The reaction was then repeated in the presence of 1.00 equiv of an additive bearing a functional moiety that either (a) required a lengthy synthesis to append onto the starting allenic ester, (b) is known to bind to and deactivate a palladium catalyst, or (c) is a potentially competitive coupling partner that could react with the boron reagent. While Glorious' protocol utilized GC analysis relative to an internal standard to determine reaction conversion and yield, the results listed in Table 2 reflect isolation of *both* the product and the additive.

Table 2. Robustness Screen as a Measure of Functional Group Tolerance/Compatibility



entry	additive	additive recovered (%)	product **30** (%)
1	none	none	87
2		91	83
3		91	88
4	*(R)*- 	95	87
5		89	91
6		95	87
7		69	83
8		93	94
9	*(S)*- 	86	90
10		88	86

As shown in Table 2, each additive was recovered in high yield and showed no inhibitory effect on the desired transformation allowing for high yields of the desired diene. Competitive insertion by Pd into an aryl bromide or triflate was not observed (entries 2, 4, and 8). Likewise, free amides, indoles, and lactams remained untouched under these conditions. Only the highly functionalized *N*-propargylic amide (entry 7) was recovered in *relatively* low yield, albeit without affecting the efficiency of diene formation. Nonetheless, given all the possibilities for participation by this additive (e.g., oxidative addition, nitro reduction, directed *ortho*-C−H activation, Sonogashira-type insertion, acetylenic π-coordination, etc.), an isolated additive recovery yield of 69% was still achieved. Most notable, however, is the exceedingly high reactivity of π-allenyl intermediates, which was confirmed via entry 10, where the desired transformation of allenic benzoate **20** took place with complete selectivity over the analogous allylic benzoate. From analysis of the results described above, general reactivity patterns can be deduced. Thus, the order of reactivity associated with standard reagents used in micellar cross-coupling reactions can be summarized, as shown in Figure 1.

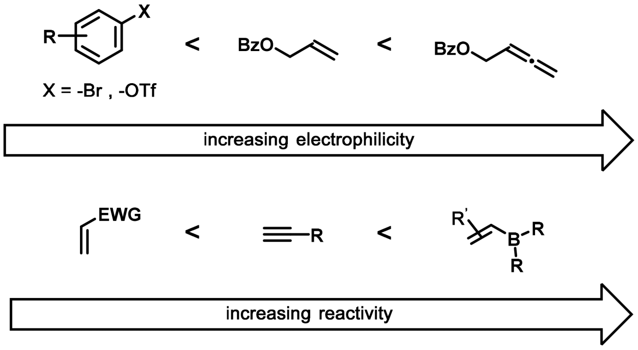


Figure 1. Order of reactivity in Pd-catalyzed cross-couplings in micellar media.

In conclusion, a mild and environmentally responsible methodology has been developed as a general strategy to access substituted 1,3-butadienes utilizing palladium catalysis under micellar reaction conditions. The technology allows for facile formation of new C−C bonds of an sp−sp^2, sp^2−sp^2, or sp^2−sp^3 nature exclusively at the 2-position of the resulting diene. Moreover, both functional group tolerance and chemoselectivity appear to be high. These developments expand the toolbox of technologies now available and further attest to the myriad of possibilities that lie ahead within the new world of organic synthesis in water.[6c,14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01377.

> Reaction optimization; details of experiments, analytical data for all new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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