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# Synthesis of 1,3-Dienes via a Sequential Suzuki–Miyaura Coupling/Palladium-Mediated Allene Isomerization Sequence

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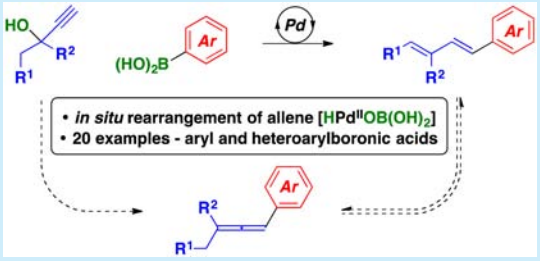
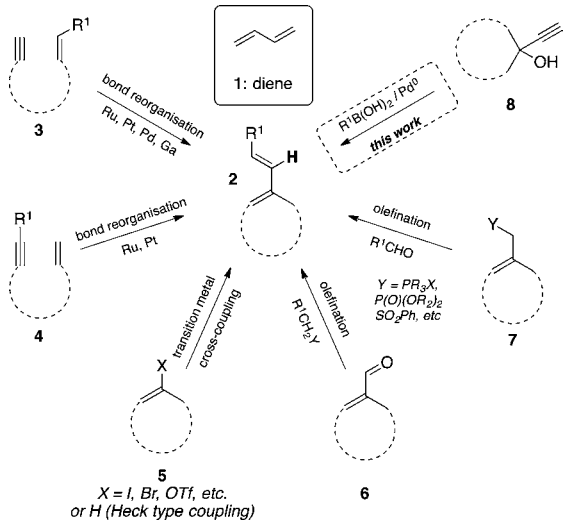
Supporting Information

**ABSTRACT:** We report a facile method for the synthesis of 1,3-dienes by a sequential process consisting of a palladium-catalyzed, base-free, Suzuki–Miyaura coupling/isomerization sequence. This sequence couples boronic acids with propargyl alcohols, generating the requisite allene *in situ*, followed by conversion of the unactivated allene to its 1,3-diene via a hydro-palladation/dehydro-palladation process. This process is general for a range of boronic acids, including boronic acids with electron-donating and -withdrawing groups, as well as heteroarylboronic acids. Key to this process is the boric acid byproduct of the base-free Suzuki–Miyauru coupling, which generates the required palladium–hydrido complex [H–Pd$^{II}$–OB(OH)$_2$] required for the isomerization.




The 1,3-diene motif is one of the most important and ubiquitous structural units in organic chemistry (Scheme 1, **1**). It has been at the cornerstone of many of the most

**Scheme 1. Synthesis of 1,3-Dienes**

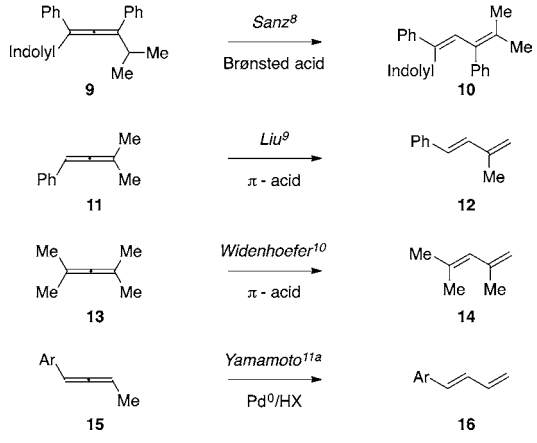



significant synthetic transformations within the discipline (e.g., Diels–Alder, pericyclic transformations); it is present in numerous natural products and drug candidates, and as such any new synthetic method that can greatly simplify its synthesis is noteworthy.[1]

1,3-Dienes (**2**) of the structure shown in Scheme 1, whether cyclic or acyclic, can be synthesized via a number of methods including (i) bond reorganization of eneyne substrates (**3** and **4**) using transition or noble metal catalysis,[2] (ii) traditional metal cross-coupling of a suitably functionalized precursor (**5**),[3] and (iii) olefination methods on substrates such as **6** and **7**.[4] An additional, atom-efficient approach is the rearrangement of an alkyl-substituted allene[5] (**8**) to a diene (**2**), via a formal 1,3-hydrogen migratory process (Scheme 1).

This type of 1,3-hydrogen migratory route, under either kinetic or thermodynamic conditions, is commonly found in activated allenes;[6] however, such transformations on unactivated allenes have been infrequent within the literature.[7] Reported procedures include the use of Brønsted acids by Sanz[8] in 2010 (Scheme 2); Au(I) $\pi$-acids by Liu[9] in 2012 and Widenhoefer in 2014,[10] where the latter were able to isolate and crystallize the Au(I) $\pi$-1,3-diene complex; and Yamamoto in 1998[11a] who demonstrated that aliphatic allenes could be isomerized using a Pd$^0$/acetic acid protocol to their 1,3-dienes,

**Scheme 2. Reported Conversion of Allenes to 1,3-Dienes**

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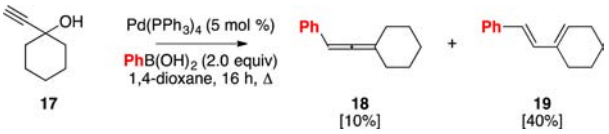
but with a very limited substrate scope, moderate yields, and with a competing hydrocarboxylation pathway.

With these examples of formal 1,3-hydrogen migration routes to 1,3-dienes from allenes in mind, we would now like to report an operationally simple route to 1,3-dienes such as **2**. This method involves a palladium-mediated, base-free, Suzuki–Miyaura coupling of propargyl alcohols (**8**) and boronic acids to give the required unactivated allene,[12] followed by a novel *in situ* rearrangement of this allene to give the sought after 1,3-diene. Furthermore, the rearrangement of the unactivated allene to the 1,3-diene involves an *in situ* hydropalladation/dehydropalladation step promoted by the formation of boric acid within the base-free Suzuki–Miyaura reaction conditions.

Our initial detection of this transformation occurred when **17** was exposed to the adapted conditions of Yoshida and co-workers (Scheme 3),[12] where extended heating of this reaction

**Scheme 3. Unexpected Formation of 1,3-Diene 3**




led not to the exclusive isolation of the allene **18**, but to significant amounts of the 1,3-diene **19** in an isolated yield of 40%. The product **19** was confirmed by a combination of $^{1}$H, $^{13}$C NMR and IR spectroscopy, with *inter alia* a coupling of $J$ = 16 Hz between alkene protons at 6.85 and 6.52 ppm, respectively, indicative of an *E*-double bond.

The formation of the allene precursor has previously been optimized by Yoshida;[12] however, a small focused optimization for this transformation was performed (Table 1). In line with

**Table 1. 1,3-Diene Optimization Conditions**[a]

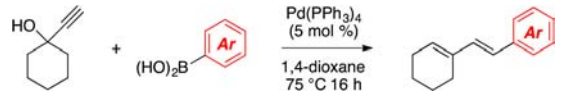
| entry | $PhB(OH)_2$ (equiv) | solvent | temp [°C] | conversion to **19**[b] [%] |
|---|---|---|---|---|
| 1 | 3 | THF | reflux | 5 |
| 2 | 3 | $CH_3CN$ | 75 | – |
| 3 | 3 | PhMe | 75 | – |
| 4 | 3 | 1,4-dioxane | reflux | 45 |
| 5 | 3 | 1,4-dioxane | 75 | 85 [78][c] |
| 6 | 3 | 1,4-dioxane | 60 | 15 |
| 7 | 2 | 1,4-dioxane | 75 | 45 |
| 8 | 1 | 1,4-dioxane | 75 | 20 |

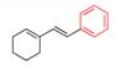
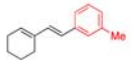
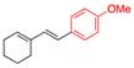
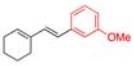
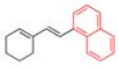
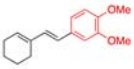
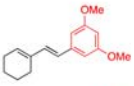
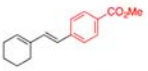
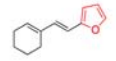
[a]Reactions were performed under a $N_2$ atmosphere at 0.5 M, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated. [b]Determined by $^{1}$H NMR. [c]Isolated yield.

Yoshida,[12] 1,4-dioxane proved optimal with THF, $CH_3CN$, and PhMe providing minimal or nil conversion (entries 1–3). Temperature was crucial for this process, with 1,4-dioxane at 75 °C proving ideal (entry 5), with a lower temperature of 60 °C giving poor conversion (entry 6) and a higher temperature (reflux) in this solvent providing significant amounts of degradation products and therefore lower conversion (entry 4). The number of equivalents of boronic acid was also probed (entries 7 and 8) with 3 equiv proving optimal, unlike Yoshida and co-workers who found 2 equiv to be favorable.

With conditions for this transformation established, we next looked at the scope of this reaction with regard to the boronic acid coupling partner (Table 2). Electron-rich boronic acids all

**Table 2. Variation of the Arylboronic Acid**[a]




| entry | (HO)$_2$B–Ar | 1,3-diene product | | yield [%][b] |
|---|---|---|---|---|
| 1 |  |  | **19** | 78 |
| 2 |  |  | **20** | 99 |
| 3 |  |  | **21** | 87 |
| 4 |  |  | **22** | 60 |
| 5 |  |  | **23** | 94 |
| 6 |  |  | **24** | 57 |
| 7 |  |  | **25** | 62 |
| 8 |  |  | **26** | 70 |
| 9 |  |  | **27** | 66 |
| 10 |  | - | **28** | <5[c] |

[a]Reactions were performed under a $N_2$ atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated. [b]Isolated yields unless otherwise stated. [c]Determined by $^{1}$H NMR spectroscopy.

participated in the transformation with moderate to high isolated yield (entries 2–4). 1-Naphthylboronic acid performed well, giving the 1,3-diene (**23**) in 94% yield (entry 5), as did 3,4-dimethoxyphenylboronic acid, which gave the 1,3-diene (**24**) in 57% yield (entry 6), and 3,5-dimethoxyphenylboronic acid, which gave **25** in 62% isolated yield (entry 7). A boronic acid containing an electron-withdrawing group was tolerated under the reaction conditions, giving the 1,3-diene **26** in 70% yield (entry 8). A heterocyclic boronic acid was also tolerant of the reaction conditions, with 2-furanylboronic acid giving **27** in 66% isolated yield (entries 9); however, 4-bromophenylboronic acid gave limited amounts of the 1,3-diene, with a significant amount of starting alkyne and polymeric material being detected (entry 10).

Next we examined variation of the alkyne coupling partner in this transformation (Table 3). Cyclopentyl propargyl alcohol **29** performed equally well with phenyl, 4-methyl, and 4-methoxyboronic acid giving the 1,3-dienes **30**, **31**, and **32**, respectively (entries 1–3). Furthermore, cycloheptyl- (**33**) and cyclooctyl- (**35**) also behaved as expected to give 1,3-dienes **34** and **36**, in yields of 80% and 75%, respectively (entries 4 and 5).

The 1,4-dioxaspiro-protected propargyl alcohol **37**, when coupled with 3,5-dimethoxyphenylboronic acid, gave the 1,3-



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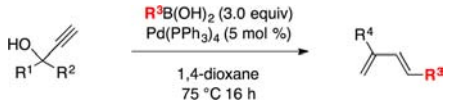
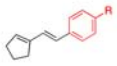
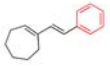
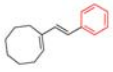
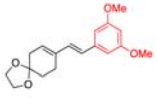
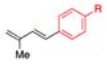
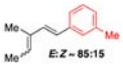
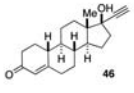
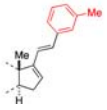
**Table 3. Variation of the Propargyl Alcohol**[a]



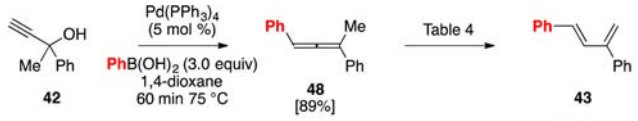

| entry | propargyl alcohol | 1,3-diene product | | yield [%][b] |
|---|---|---|---|---|
| 1 | | | **30**:R = H | 61 |
| 2 |  |  | **31**:R = Me | 67 |
| 3 | | | **32**:R = OMe | 78 |
| 4 |  |  | **34** | 80 |
| 5 |  |  | **36** | 75 |
| 6 |  |  | **38** | 43 |
| 7 | | | **40**:R = H | 85 |
| 8 |  |  | **41**:R = Me | 47 |
| 9 |  |  | **43** | 74 |
| 10[c] |  |  | **45** | 55 |
| 11 |  |  | **47** | 64 |

[a]Reactions were performed under a $N_2$ atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated. [b]Isolated yields unless otherwise stated. [c]Isolated as a mixture of *E*- and *Z*-isomers in approximately 85:15 ratio.

diene **38** in a moderate yield of 47%, demonstrating that the reaction is tolerant of acid sensitive functional groups (entry 6). The acyclic propargyl alcohols 2-methyl-3-butyn-2-ol **39**, when exposed to phenylboronic acid, gave 1,3-diene **40** in 85% yield, while 4-tolylboronic acid gave 1,3-diene **41** in a modest 47% yield (entries 7 and 8). Similarly, 2-phenyl-3-butyn-2-ol **42** gave the 1,3-diene **43** in 74% isolated yield when exposed to phenylboronic acid (entry 9). To investigate the selectivity of this reaction, with regard to 1,3-diene formation, 3-methyl-1-pentyn-3-ol **44** was exposed to 3-methyphenylboronic acid, yielding the 1,3-diene **45**[13] as the predominant product in 55% yield (entry 10). The predominance of this 1,3-diene **45** in this example is presumably due to the formation of the trisubstituted alkene as the thermodynamic product. Finally, 19-norethistrone **46** was exposed to the reaction conditions with 3-methylphenylboronic acid, yielding the 1,3-diene **47** in 64% yield, therefore giving an ideal handle for further functionalization of this important steroid (entry 11).

To demonstrate that this process is two-step, i.e., conversion of the alkyne to an allene followed by rearrangement to its 1,3-diene, the reaction was monitored for the formation of allene **48**,[14] which was subsequently isolated in 89% yield (Scheme 6). With **48** in hand we then exposed it to reaction conditions, mirroring those in Table 1, to promote the formation of 1,3-diene **43** (Table 4). The exposure of **48** to 5 mol % of $Pd^0$ gave

**Table 4. Allene Isomerization**[a]




**42** **48** [89%] **43**

| entry | additive[b] | catalyst[c] | product[d] [%] **48** | product[d] [%] **43** |
|---|---|---|---|---|
| 1 | - | $Pd(PPh_3)_4$ | 90 | - |
| 2 | $PhB(OH)_2$ | - | 90 | - |
| 3 | $PhB(OH)_2$ | $Pd(PPh_3)_4$ | 52 | 15 |
| 4 | $B(OH)_3$ | - | 90 | - |
| 5 | $B(OH)_3$ | $Pd(PPh_3)_4$ | >5 | 92 [86][e] |
| 6 | BzOH | $Pd(PPh_3)_4$ | >5 | 60[e] |

[a]Reactions were performed under a $N_2$ atmosphere at 0.5 M in 1,4-dioxane for 16 h unless otherwise stated. [b]100 mol %. [c]5 mol %. [d]Determined by $^1H$ NMR. [e]Isolated yield.

no conversion, with only the starting allene being detected (entry 1), while exposure to phenyboronic acid mirrored that of entry 1 (entry 2). Phenylboronic acid in the presence of $Pd^0$ did give a small conversion to the diene **43**, but with significant degradation of the allene and addition products[11a] being observed (entry 3).

In the acid mediated rearrangement of allenes, reported by Sanz and co-workers,[8] pTSA was used to facilitate the rearrangement of the allene. To investigate this, **48** was exposed to 1 equiv of $B(OH)_3$, the only other significantly acidic byproduct of the Suzuki–Miyaura reaction, but this failed to deliver the 1,3-diene (entry 3). This is unsurprising given the $pK_a$ of boric acid compared to pTSA. However, when **48** was exposed to $Pd^0$ and 1 equiv of $B(OH)_3$, conversion to the 1,3-diene was significant, giving **43** in 86% conversion presumably via the formation of a $H–Pd^{II}$-$OB(OH)_2$ complex (entry 5). Yamamoto and co-workers[11a,15] have reported a similar hydroalkoxylation/isomerization of allenes and alkynes using analogous $H–Pd^{II}–OBz$ and $H–Pd^{II}–OAc$ complexes, but with limited selectivity and scope. As a consequence, we exposed allene **48** to $H–Pd^{II}–OBz$, derived from $Pd^0$ and BzOH, and this gave the 1,3-diene **43**, but with a significant hydroalkoxylation byproduct (entry 6).

Given the results in Table 4, coupled with the reported mechanism[12] for the formation of the allene, we have proposed a plausible mechanism for the formation of the 1,3-diene (Scheme 4). Activation of **49** via a proton or the Lewis acidic boronic acid delivers **50**, which in the presence of $Pd^0$ undergoes nucleophilic addition to give the allenylpalladium species **51**, followed by a subsequent Suzuki–Miyaura coupling to deliver the intermediate allene **53**. We then propose, based on the results within Table 4, that the boric acid oxidizes the resultant $Pd^0$ to give the $Pd^{II}$ species $H–Pd^{II}–OB(OH)_2$ **54**. Allene **53** can then undergo hydropalladation with **54** to deliver either **55** or **56**: with **55** experiencing a dehydropalladation to regenerate the allene **53**. However, unlike **55**, **56** can undergo two possible dehydropalladations, either regenerating the allene **53** or, more significantly, delivering the observed 1,3-diene **57**.



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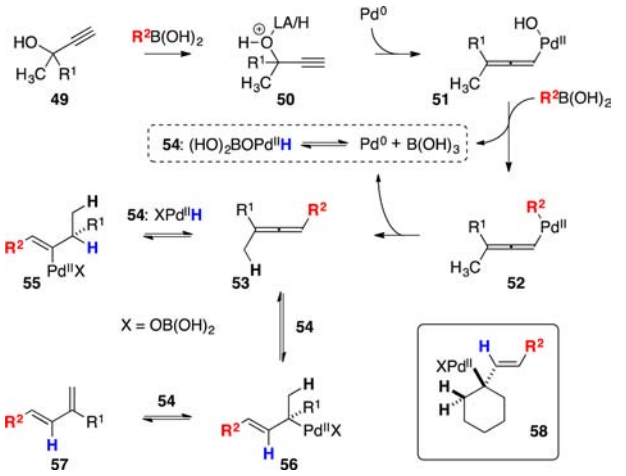
**Scheme 4. Proposed Mechanism for the Formation 1,3-Dienes from Propargyl Alcohols and Boronic Acids under Palladium Mediated Catalysis**




It should be noted that while the proposed H–$Pd^{II}$–$OB(OH)_2$ complex parallels related complexes (e.g., H–$Pd^{II}$–OBz and H–$Pd^{II}$–OAc) as reported by Yamamoto,[11a,15] it displays a *significant* divergence in reactivity. Whereas the latter complex when reacted with allenes gives the hydroalkoxylation product, presumably due to the nucleophilicity of the benzoate conjugate base, the former H–$Pd^{II}$–$OB(OH)_2$ complex gives predominantly the rearranged 1,3-diene product.

In summary, we have developed a two-step sequential synthesis of 1,3-dienes from propargyl alcohols and arylboronic acids. This sequence gives an initial intermediary unactivated allenyl precursor, via a base-free Suzuki–Miyaura coupling, which undergoes a subsequent rearrangement to its 1,3-diene, facilitated by the *in situ* formation of a H–$Pd^{II}$–$OB(OH)_2$ complex. The reaction is general for a range of boronic acids and propargyl substrates and exhibits moderate to high chemical yields. Further efforts will be directed toward understanding and utilizing this H–$Pd^{II}$–$OB(OH)_2$ complex in alkenyl, allenyl, and alkynyl rearrangements.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01841.

Experimental procedures, NMR spectra, and characterization for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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