Synthesis of 1,3-dienes *via* a sequential Suzuki-Miyaura coupling-palladium mediated allene isomerization sequence

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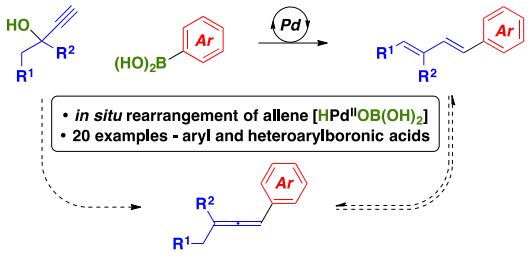
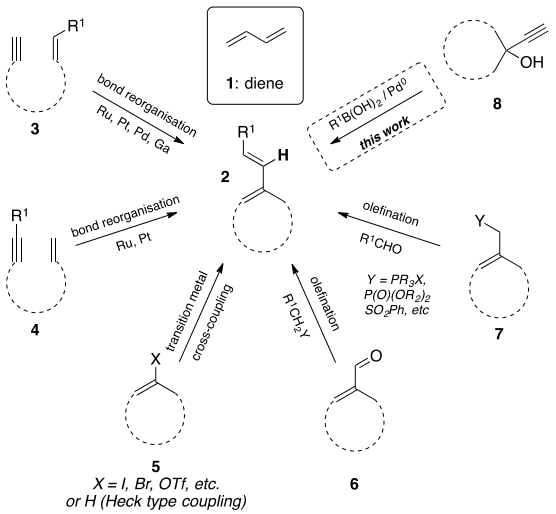
Supporting Information Placeholder



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 by-product of the base-free Suzuki–Miyauru coupling, which generates the required palladium–hydrido complex [H-Pd^{II}-OB(OH)$_2$] required for the isomerization.

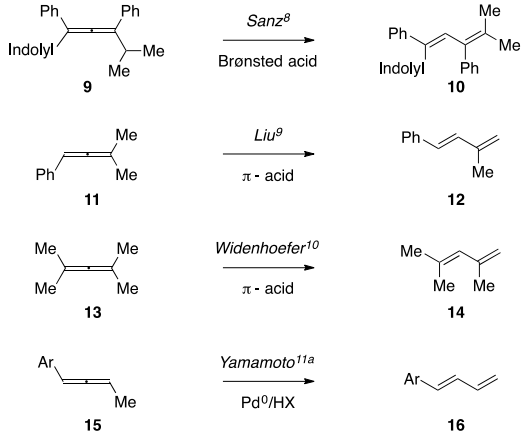
The 1,3-diene motif is one of the most important and ubiquitous structural units in organic chemistry (Scheme 1, **1**). It has been at the cornerstone of many of the most significant synthetic transformations within the discipline (e.g., Diels-Alder, pericyclic transformations); it is present in numerous natural products and drug candidates, and as such any new synthetic method that can greatly simplify its synthesis is noteworthy.[1]

Scheme 1. Synthesis of 1,3-dienes.



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 reorganisation 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] as well as (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).

Scheme 2. Reported conversion of allenes to 1,3-dienes.



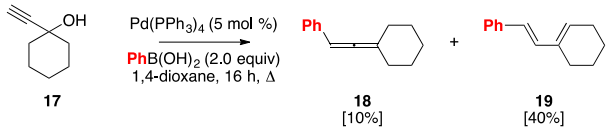
This type of 1,3-hydrogen migratory route, either under kinetic or thermodynamic conditions, is commonly found in activated allenes,[6] however, such transformations on unactivated allenes have been infrequent within the literature.[7] Reported procedures include the use of Brønsted acids by Sanz[8] in 2010; Au(I) π-acids by Liu[9] in 2012 and Widenhoefer in 2014,[10]

where the latter were able to isolate and crystallize the Au(I) π-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, but with 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 led not to the exclusive isolation of the allene **18**, but significant amounts of the 1,3-diene **19** in an isolated yield of 40%. The product **19** was confirmed by a combination of ^1H, ^{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.

Scheme 3. Unexpected formation of 1,3-diene 3.



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 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 proving optimal, unlike Yoshida and co-workers who found two equivalents to be favorable.

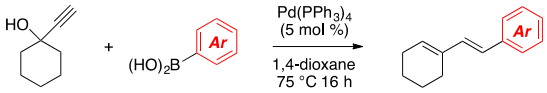
Table 1. 1,3-Diene optimization conditions.[a]

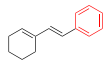
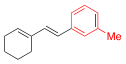
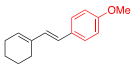
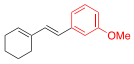
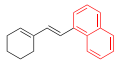
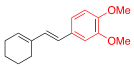
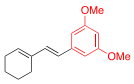
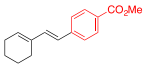
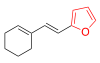
entry	$PhB(OH)_2$ (equiv)	solvent	temp [°C]	conversion to **19**[b] [%]
1	3	THF	reflux	5
2	3	CH_3CN	75	-
3	3	PhMe	75	-
4	3	1,4-dioxane	reflux	45
5	3	1,4-dioxane	75	85 [78][c]
6	3	1,4-dioxane	60	15
7	2	1,4-dioxane	75	45
8	1	1,4-dioxane	75	20

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

With conditions for this transformation established, we next looked at the scope of this reaction with regard to the boronic acid coupling partner (Scheme 4 and Table 2). Electron rich boronic acids all 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 significant amount of starting alkyne and polymeric material being detected (entry 10).

Table 2.[a] **Variation of the arylboronic acid.**



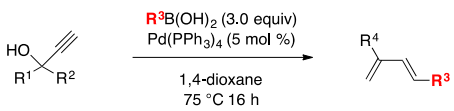
entry	(HO)$_2$B–Ar	1,3-diene product		yield [%][b]
1			**19**	78
2			**20**	99
3			**21**	87
4			**22**	60
5			**23**	94
6			**24**	57
7			**25**	62
8			**26**	70
9			**27**	66
10		-	**28**	<5[c]

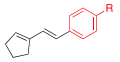
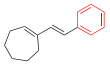
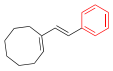
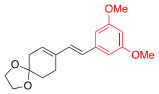
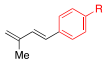
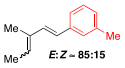
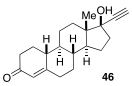
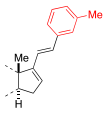
[a]Reactions were performed under N_2 atmosphere at 0.5 M in 1,4-dioxane, with 5 mol % of $Pd(PPh_3)_4$ for 16 h, unless otherwise stated. [b]Isolated yields unless otherwise stated. [c]Determined by ^1H NMR spectroscopy.

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).

Table 3.[a] Variation of the propargyl alcohol.



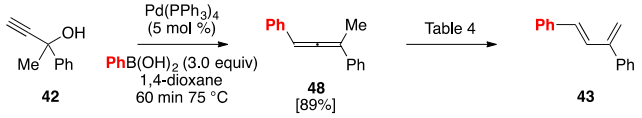
entry	propargyl alcohol	1,3-diene product		yield [%][b]
1			**30**:R = H	61
2	 **29**		**31**:R = Me	67
3			**32**:R = OMe	78
4	 **33**		**34**	80
5	 **35**		**36**	75
6	 **37**		**38**	43
7			**40**:R = H	85
8	 **39**		**41**:R = Me	47
9	 **42**		**43**	74
10[c]	 **44**	 *E*:*Z* – 85:15	**45**	55
11	 **46**		**47**	64

[a]Reactions were performed under 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 approx. 85:15 ratio.

The 1,4-dioxaspiro-protected propargyl alcohol **37**, when coupled with 3,5-dimethoxyphenylboronic acid gave the 1,3-diene **38** in 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** (Scheme 4 and Table 4). The exposure of **48** to 5 mol % of Pd^0 gave 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).

Scheme 4 and Table 4.[a] Allene isomerization.



42 → **48** [89%] → **43**

entry	additive[b]	catalyst[c]	product[d] [%]	
			48	**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]

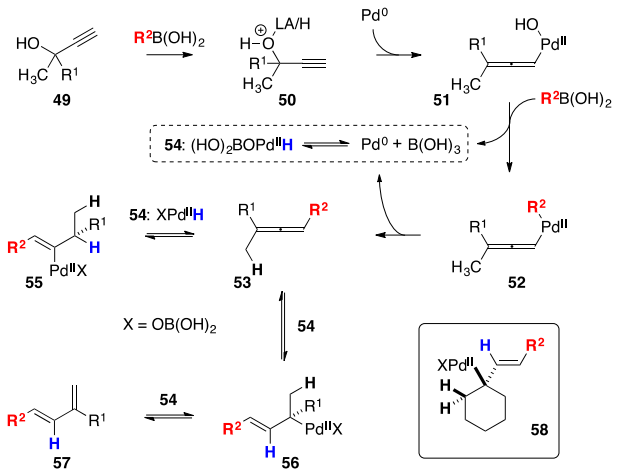
[a]Reactions were performed under N_2 atmosphere at 0.5 M in 1,4-dioxane for 16 h unless otherwise stated. [b]100 mol %. [c]5 mol %. [d]Determined by ^1H NMR. [e]Isolated yield.

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 $B(OH)_3$, the only other significantly acidic by-product of the Suzuki-Miyaura reaction, but this failed to deliver the 1,3-diene (entry 3). This is unsurprising given the pKa 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 significant hydroalkoxylation by-product (entry 6).

Given the results in Table 3, 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 5). 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 3, 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**.

Scheme 5. 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

Experimental procedures, NMR spectra and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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