



Synthesis of highly substituted 1,3-dienes, 1,3,5-trienes, and 3,6-disubstituted cyclohexenes by the palladium-catalyzed coupling of organic halides, internal alkynes or 1,3-cyclohexadienes, and organoboranes

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ABSTRACT

A number of highly substituted 1,3-dienes and 1,3,5-trienes have been stereoselectively prepared in moderate to good yields by the coupling of vinylic iodides, internal alkynes, and organoboranes in the presence of a palladium catalyst. Optimal reaction conditions for different organoboron substrates have been developed. The analogous three-component coupling of aryl halides, 1,3-cyclohexadiene, and boronic acids provides a synthetically useful route to 3,6-disubstituted cyclohexenes. These methods are very efficient and provide an expeditious way to synthesize the indicated alkenes, dienes, and trienes, whose preparation would normally require multi-step synthesis.

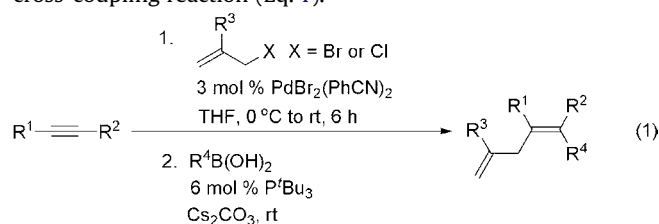
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1. Introduction

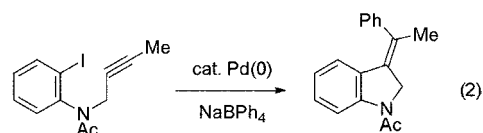
1,3-Dienes and 1,3,5-trienes are important products or intermediates in organic chemistry.¹ They are of great interest for their photochemical, electrochemical, and biological properties.² While there are numerous previous methods to prepare simple dienes and trienes, the regio- and stereoselective construction of highly-substituted dienes and trienes, and especially those bearing tetrasubstituted double bonds, remains one of the biggest challenges in organic synthesis.³ Therefore, a strategic and diverse approach to such olefins is highly desirable.

The propensity of unsaturated compounds, such as alkenes, allenes, 1,3-dienes, and alkynes, to undergo insertion into carbon–metal bonds makes these substrates some of the most useful for transition metal-catalyzed organic transformations.⁴ Organoboronic acids and borates are widely used in the palladium-catalyzed Suzuki coupling with organic halides, providing an extremely useful route for carbon–carbon bond formation.⁵ Thus, the palladium-catalyzed sequential ternary coupling of organic halides, unsaturated compounds, and organoboronic acids is expected to be a highly efficient process employing multiple reaction steps in a single pot. The practical advantage of the Suzuki reaction compared with other coupling reactions lies in the fact that boronic acids are readily prepared, non-toxic and thermally, air, and moisture stable, as well as being compatible with diverse functional groups.

Rawal et al. have reported the synthesis of skipped dienes by the palladium-catalyzed allylation of alkynes and a subsequent Suzuki cross-coupling reaction (Eq. 1).⁶



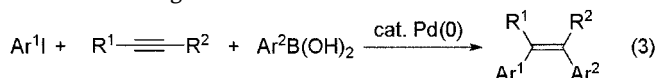
Grigg et al. have synthesized polycyclic compounds bearing a substituted 1,3-diene moiety through the intramolecular tandem reaction of an aromatic halide with an internal alkyne, followed by cross-coupling with an external arylborate (Eq. 2).⁷ We have



previously reported⁸ a highly efficient, stereo- and regioselective synthesis of tetrasubstituted olefins by the palladium-catalyzed cross-coupling of aryl halides, internal alkynes, and arylboronic acids (Eq. 3). Herein, we report full details of our investigation of

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a one-pot, intermolecular palladium-catalyzed coupling of vinylic halides, internal alkynes, and aryl or vinylic boron organometallics, which offers an efficient, direct route for the construction of a number of highly substituted 1,3-dienes or 1,3,5-trienes in a chemo-, regio-, and stereoselective manner from simple, readily available starting materials.⁹




2. Results and discussion

2.1. Optimization

Our initial work was aimed at developing a set of reaction conditions that would work well for a variety of substrates. The reaction of vinylic iodide **1**, 1-phenylpropyne, and phenylboronic acid was chosen as the model system for optimization of this process (Eq. 4), and the results are summarized in Table 1. The

Table 1
Optimization of the reaction of vinylic iodide **1**, 1-phenylpropyne, and phenylboronic acid (Eq. 4)^a

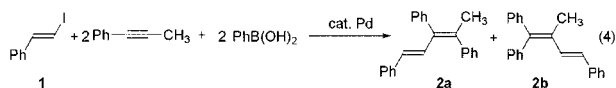
Entry	Base (equiv)	Pd catalyst	Temp (°C)	DMF/H ₂ O	% yield of 2 ^b
1	K ₂ CO ₃ (1)	PdCl ₂ (PhCN) ₂	100	5:1	45
2	K ₂ CO ₃ (1)	PdCl ₂	100	5:1	46
3	K ₃ PO ₄ (1)	PdCl ₂	100	5:1	38
4	KF (2)	PdCl ₂	100	5:1	51 ^c
5	KF (2)	PdCl ₂ (PPh ₃) ₂	100	5:1	25
6	KF (2)	PdCl ₂ , 2 	100	5:1	16
7	KF (2)	Pd ₂ (dba) ₃	100	5:1	45
8	KF (2)	PdCl ₂	80	5:1	40
9	KF (2)	PdCl ₂	rt ^d	5:1	29
10	KF (2)	PdCl ₂	100	7:1	37
11	KF (2)	PdCl ₂	100	100:0	32
12	KF (2)	PdCl ₂	100	5:2	23

^a All reactions were run using 0.25 mmol of iodide **1**, 0.5 mmol of alkyne, and 0.5 mmol of phenylboronic acid, employing 5 mol% of the Pd catalyst, plus 10 mol% of a phosphine in 10 mL of DMF/H₂O for 2 h unless otherwise specified.

^b Two regioisomers were observed in all cases.

^c The two regioisomers were obtained in a 40:60 (**2a**:**2b**) ratio.

^d The reaction was incomplete after 24 h, and the two regioisomers were obtained in a 37:63 (**2a**:**2b**) ratio.



original set of reaction conditions used included 5 mol% PdCl₂(PhCN)₂, 1 equiv of K₂CO₃, and 5:1 DMF/H₂O as the solvent at 100 °C in the presence of air, conditions which were developed⁸ for our previous three-component coupling reaction of aryl halides, internal alkynes, and arylboronic acids (entry 1, Table 1). Here, we have chosen the vinylic iodide as the limiting reagent simply because it is generally less readily available and usually must be prepared in the lab, while many alkynes and boronic acids are commercially available.

Using PdCl₂ as a catalyst gave a yield comparable to that of PdCl₂(PhCN)₂ (Table 1, compare entries 1 and 2). Using PdCl₂ as the palladium source and K₃PO₄ as a base resulted in a lower yield

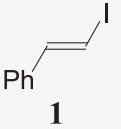
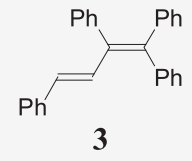
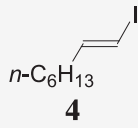
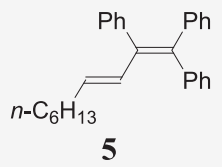
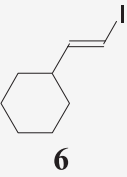
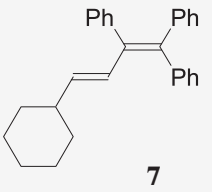
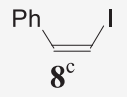
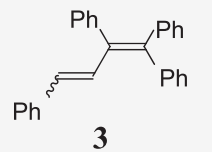
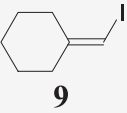
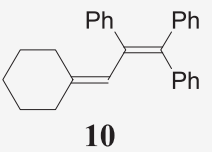
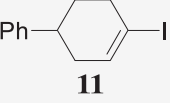
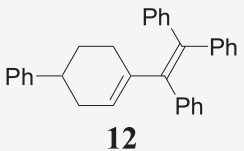
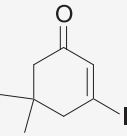
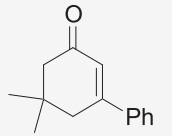
(entry 3). However, the use of KF as the base improved the yield (entry 4). The weak basicity and poor nucleophilicity of the fluoride ion could make this base particularly useful in the case of base-sensitive substrates. Adding triphenylphosphine or tri-2-furylphosphine as ligands slowed down the reaction and lowered the yield (entries 5 and 6). Using a Pd(0) catalyst, Pd₂(dba)₃, provided a yield similar to that of PdCl₂ (entry 7). Contrary to our previous observations that much better regioselectivities for the coupling of aryl iodides, internal alkynes, and boronic acids could be achieved at room temperature,⁸ a higher reaction temperature here not only shortened the reaction time, it gave a better yield than the room temperature reaction, although the effect of the reaction temperature on the regioselectivity of the reaction is minimal (compare entries 4 and 9). We, therefore, chose 100 °C as the optimal reaction temperature. The presence of water greatly facilitates the desired reaction (entries 10 and 11), perhaps because water is needed to dissolve the KF base, and F[−] or OH[−] ion most likely combines with the arylboronic acid to form an 'ate complex', which is crucial in Suzuki cross-coupling reactions.^{5,10} With insufficient water, substantial amounts of fulvenes are formed by the double insertion of alkynes, followed by ring closure, without the involvement of the boronic acid.¹¹ However, too much water facilitates the direct Suzuki reaction of the vinylic iodide and the arylboronic acid and is detrimental to the yield of the desired three-component coupling product (entry 12). We thus settled on the following 'optimal' conditions A, employing 1 equiv of vinylic halide, 2 equiv of internal alkyne, 2 equiv of arylboronic acid, 5 mol% of PdCl₂, 2 equiv of KF, and 5:1 DMF/H₂O as the solvent at 100 °C in the presence of air (the conditions of entry 5 in Table 1).

This 'optimal' procedure has thus been employed on a variety of representative substrates, which were carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems. While the yields from this model system are not particularly high, subsequent research established that our 'optimal' procedure actually works quite well when a number of different vinylic halides, alkynes, and boronic acids are employed (Table 2).

2.2. Scope of the vinylic halide

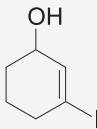
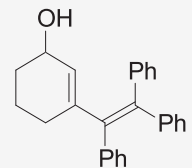
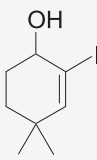
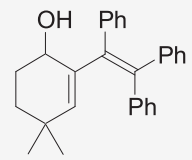
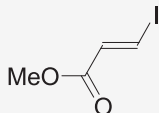
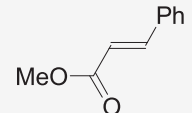
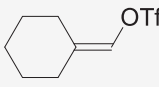
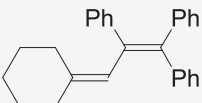
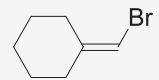
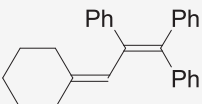
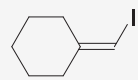
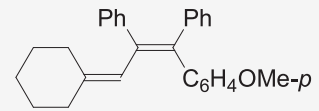
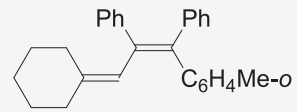
The scope and limitations of this reaction for the synthesis of a wide variety of 1,3-dienes is indicated in Table 2. Moderate yields of the desired 1,3-dienes were obtained from the reaction of β-monosubstituted *trans*-vinylic iodides (entries 1–3, Table 2) with diphenylacetylene and phenylboronic acid. In all of these reactions, we were also able to isolate 20–30% of the product from direct coupling of the vinylic iodides and phenylboronic acid, together with small amounts of tetraphenylethene, which is apparently formed by the reaction of phenylboronic acid and diphenylacetylene.¹² In all cases, geometrically pure dienes were obtained when using (*E*)-alkenes as determined by GC–MS and ¹H and ¹³C NMR spectroscopy. When an 86:14 mixture of *Z*- and *E*-β-iodostyrene was employed, a 2.5:1 mixture of the corresponding *E*- and *Z*-stereoisomeric 1,3-dienes was obtained, indicating substantial loss of stereochemistry during this particular coupling process. The thermodynamically more stable and configurationally inverted *E*-isomer **3** was generated as the major isomer (entry 4). The desired reaction proceeded very efficiently when the β,β-disubstituted vinylic iodide **9** and 1-iodo-4-phenylcyclohexene (**11**) were employed (entries 5 and 6). However, the reaction of 3-iodo-5,5-dimethylcyclohex-2-enone (**13**) and diphenylacetylene afforded a product in which the vinylic halide and arylboronic acid had undergone direct cross-coupling without insertion of the alkyne (entry 7). None of the desired 1,3-diene was observed. Obviously, an electron-withdrawing group on the β-position of the vinylic halide greatly facilitates direct nucleophilic transmetalation of the boronic

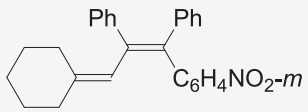
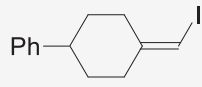
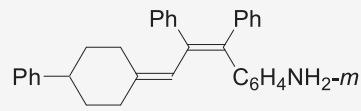
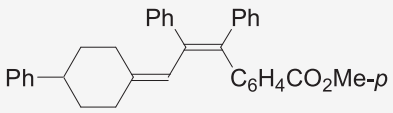
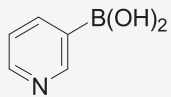
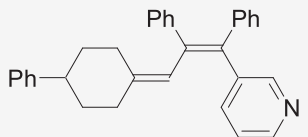
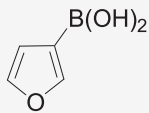
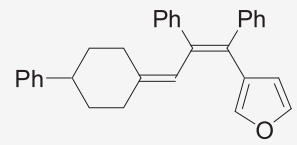
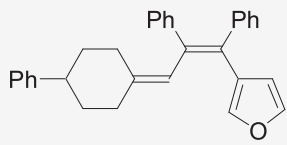
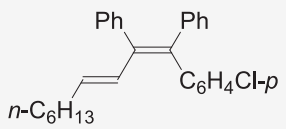
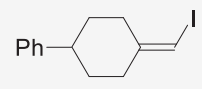
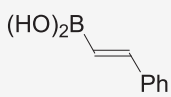
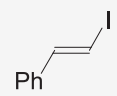
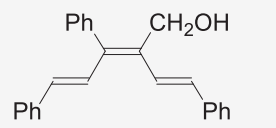
Table 2
Palladium-catalyzed three-component coupling of vinylic (aryl) halides, internal alkynes or 1,3-cyclohexadiene, and organoboranes

Entry	Halide	Alkyne or 1,3-cyclohexadiene	Organoborane	Cond., ^a time (h)	Product(s)	% yield ^b
1	 1	$\text{Ph} \text{---} \text{C} \equiv \text{C} \text{---} \text{Ph}$	PhB(OH)_2	A, 2	 3	45
2	 4			A, 2	 5	62
3	 6			A, 2	 7	54
4	 8^c			A, 2	 3	42 ^d
5	 9			A, 2	 10	87
6	 11			A, 2	 12	78
7	 13			A, 2	 14	90

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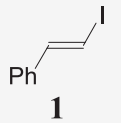
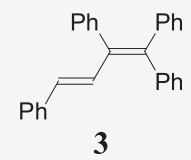
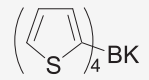
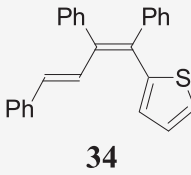
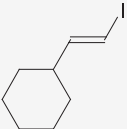
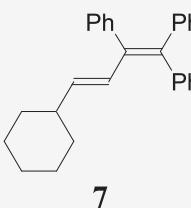
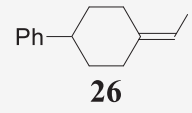
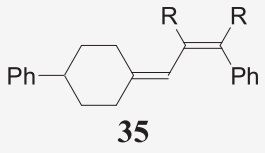
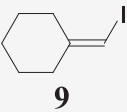
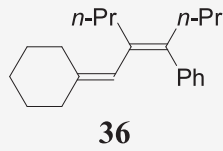
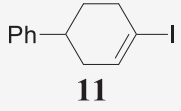
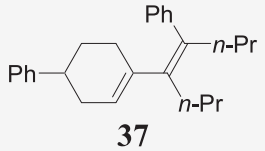
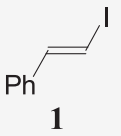
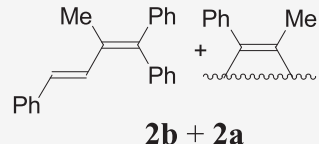
Table 2 (continued)

Entry	Halide	Alkyne or 1,3-cyclohexadiene	Organoborane	Cond., ^a time (h)	Product(s)	% yield ^b
8				A, 2		41
9				A, 2		24 ^e
10				A, 2		31
11				A, 2		30
12				A, 16		5
13		$\text{Ph} \text{---} \text{C} \equiv \text{C} \text{---} \text{Ph}$	<i>p</i> -MeOC ₆ H ₄ B(OH) ₂	A, 2		93
14			<i>o</i> -MeC ₆ H ₄ B(OH) ₂	A, 2		82

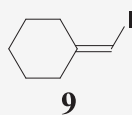
15		$m\text{-O}_2\text{NC}_6\text{H}_4\text{B}(\text{OH})_2$	A, 2		56
				25	
16		$m\text{-H}_2\text{NC}_6\text{H}_4\text{B}(\text{OH})_2$	A, 2		86
	26			27	
17		$p\text{-MeO}_2\text{CC}_6\text{H}_4\text{B}(\text{OH})_2$	A, 2		60
				28	
18			A, 2		63
				29	
19			A, 2		68
				30	
20		$p\text{-ClC}_6\text{H}_4\text{B}(\text{OH})_2$	A, 2		37
	30			31	
21		$\text{HOH}_2\text{C} \equiv \text{CH}_2\text{OH}$	A, 2		31, 57 ^f
	26				
22		$\text{Ph} \equiv \text{CH}_2\text{OH}$	A, 2		32
	1			33	

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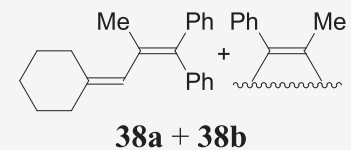
Table 2 (continued)

Entry	Halide	Alkyne or 1,3-cyclohexadiene	Organoborane	Cond., ^a time (h)	Product(s)	% yield ^b
23		$\text{Ph} \equiv \text{Ph}$	NaBPh_4	B, 12		71
24				B, 12		80
25			KBF_3Ph	A, 12		31 ^g
26		$\text{R} \equiv \text{R}$ $\text{R} = \text{C}_6\text{H}_4\text{CO}_2\text{Et}-p$	$\text{PhB}(\text{OH})_2$	A, 2		68
27		$n\text{-Pr} \equiv n\text{-Pr}$		A, 2	$n\text{-Pr} \equiv n\text{-Pr}$	85
28				A, 2		63
29		$\text{Ph} \equiv \text{Me}$		A, 2		51 ^h (60:40)

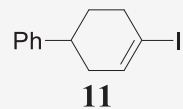
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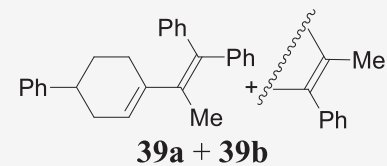
A, 2

90^h (59:41)

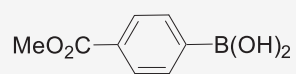
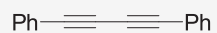
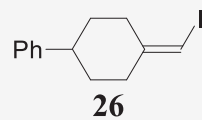
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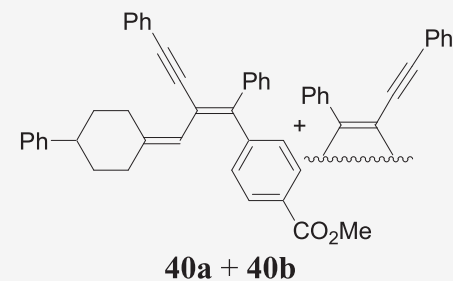
A, 2

71^{hi} (56:44)

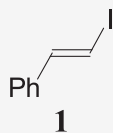
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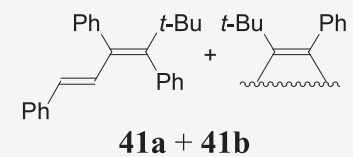
A, 2

62^h (88:12)

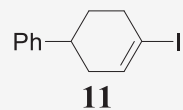
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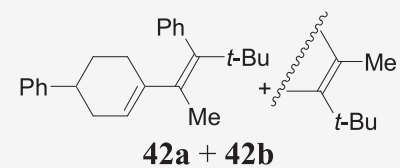
A, 2

60^{hj} (85:15)

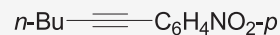
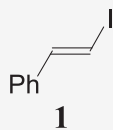
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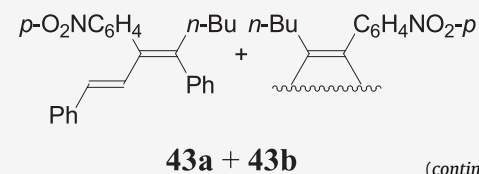
A, 2

35^h (95:5)

35



A, 2

62^h (86:14)

(continued on next page)

Table 2 (continued)

Entry	Halide	Alkyne or 1,3-cyclohexadiene	Organoborane	Cond., ^a time (h)	Product(s)	% yield ^b
36				A, 2		60 ^b (83:17)
37		Ph-C≡C-CH(OH)Me		A, 2		93 ^{b, i} (70:30)
38		Ph-C≡C-CH ₂ OH		A, 4		85 ^{b, i} (68:32)
39		Ph-C≡C-COMe		A, 2		71 ^b (63:37)
40		Ph-C≡C-CO ₂ Et		A, 2		62 ^b (68:32)
41		Ph-C≡C-COMe		A, 2		82 ^b (71:29)

42	PhI			C, 4		58
43				C, 4		51
44	<i>p</i> -MeC ₆ H ₄ I			D, 24	50	59 ^k
45	<i>p</i> -H ₂ NC ₆ H ₄ I			D, 24	51	89
46	<i>p</i> -HOC ₆ H ₄ I			D, 24	52	70
47	<i>p</i> -MeOC ₆ H ₄ I			D, 24	53	58
48	<i>p</i> -MeCOC ₆ H ₄ I			D, 24	54	0
49	<i>o</i> -MeC ₆ H ₄ I			D, 24	55	19
50	<i>p</i> -H ₂ NC ₆ H ₄ I			<i>o</i> -MeC ₆ H ₄ B(OH) ₂	D, 24	56
51	<i>p</i> -H ₂ NC ₆ H ₄ I	<i>p</i> -ClC ₆ H ₄ B(OH) ₂	D, 24	57	53	
52				D, 24		88

^a See the text for conditions A–D.

^b Isolated yield.

^c This compound was prepared and utilized as an 86:14 mixture of *Z/E* isomers.

^d The product was obtained as a 2.5:1 mixture of *E*- and *Z*-stereoisomers.

^e A 59% yield of 4,4-dimethyl-2-phenylcyclohex-2-en-1-ol was obtained.

^f 6 equiv of KF were employed.

^g Only a trace amount of **7** was obtained without KF as the base.

^h The products are inseparable.

ⁱ The regioisomers are tentatively assigned according to the general rule for the insertion of alkynes in organopalladium reactions.

^j The reaction was run employing a ratio of iodide/alkyne/boronic acid=2:1:2.

^k The yield was determined by ¹H and ¹³C NMR spectral analysis.

acid by the organopalladium(II) intermediate, rather than alkyne insertion, resulting in the monoene product (see the later [Mechanistic discussion](#)). On the other hand, the hydroxy-containing vinylic halide **15** reacts with diphenylacetylene under our standard reaction conditions to give the desired dienol **16** in a 41% yield, which should be easily oxidized to the corresponding ketone (entry 8). Placing the halide nearer the alcohol functionality resulted in a still lower 24% yield of the desired diene **18**, alongside a 59% yield of the direct Suzuki product 4,4-dimethyl-2-phenylcyclohex-2-en-1-ol (entry 9). The presence of a vicinal OH group is apparently detrimental to carbopalladiation of the alkyne. The reaction of methyl *trans*-2-iodoacrylate generated a 31% yield of methyl cinnamate without any of the desired diene being detected. It appears that this iodide is unstable under our reaction conditions. A vinylic triflate has been cross-coupled using this process, although a much lower yield was observed than that obtained using the analogous iodide (compare entries 5 and 11). Unfortunately, the analogous vinylic bromide proved to be essentially inert in this process (entry 12). Only a 5% yield of the expected diene was formed after 16 h reaction and most of the vinylic bromide remained unreacted.

2.3. Scope of the boronic acid

A wide variety of dienes can be synthesized in excellent yields from the reaction of vinylic iodide **9**, diphenylacetylene, and various functionally-substituted arylboronic acids. For example, the electron-rich arylboronic acid *p*-methoxyphenylboronic acid (entry 13) and the relatively hindered *o*-tolylboronic acid (entry 14) gave excellent yields of dienes. However, the yield dropped considerably when a relatively electron-poor boronic acid, like 3-nitrophenylboronic acid, was employed (entry 15). The generation of substantial amounts of the direct cross-coupling product 3-nitrobenzylidenecyclohexane accounts for the decrease in the yield. Similar electronic effects have been observed in the reactions of vinylic iodide **26** and 3-aminophenylboronic acid (entry 16) and 4-methoxycarbonylphenylboronic acid (entry 17). While the former boronic acid gave an 86% yield of the desired product, the yield dropped to 60% for the latter boronic acid. We were pleased to find that important heterocyclic moieties, such as furyl and pyridyl groups, can be successfully incorporated into dienes using our procedure and the corresponding boronic acids (entries 18 and 19). Using *E*-1-iodo-1-octene and 4-chlorophenylboronic acid, instead of phenylboronic acid, resulted in the yield dropping from 62% to 37% (compare entry 2 with entry 20).

The nature of the boronic acid was expanded to alkenyl variants to generate 1,3,5-trienes. When vinylic iodide **26** was allowed to react with 2-butyne-1,4-diol and styrylboronic acid under the standard reaction conditions, triene **33** was generated in a 31% yield. The yield could be further improved to 57% when 6 equiv of KF were employed, but further increasing the equivalents of KF to 10 lowered the yield to 48% (entry 21). The synthesis of trienes utilizing β -iodostyrene has consistently given lower yields than other more substituted vinylic iodides (entry 22).

Unfortunately, extensive optimization efforts devoted toward incorporating alkyl, allyl, and cyclopropyl groups from the corresponding boronic acids or esters have proven fruitless when employing vinylic iodide **1** and diphenylacetylene. Under conditions A, all of the above boronic acids afforded products of vinylpalladium addition to the alkyne, followed by hydrogen substitution of the Pd moiety. It is unclear where the hydrogen is coming from in these reactions. We hypothesize that it might be coming from formate possibly produced by the hydrolysis of the DMF in the presence of base.¹³

Other organometallics can also be employed in these cross-coupling reactions. For example, when $\text{PhB}(\text{OH})_2$ was replaced by

NaBPh_4 , the desired diene was obtained under non-aqueous and non-basic conditions. The 'optimal' reaction conditions B for this process utilize 2 equiv of the vinylic halide, 1 equiv of the internal alkyne, 2 equiv of borate, 5 mol % of $\text{Pd}(\text{OAc})_2$, and 1 equiv of LiCl in DMF at 100 °C in the presence of air.¹⁴ Under these conditions, vinylic halide **1** reacts with diphenylacetylene and NaBPh_4 to afford the desired product **3** in a 71% yield (entry 23). Transmetalation of a thiophene group from sodium tetra(2-thiophenyl)borate was even more facile, producing **34** in an 80% yield (entry 24). The reaction of postassium phenyltrifluoroborate also provides the desired 1,3-diene **7**, but in a lower yield (compare entry 3 and 25). It is noteworthy that the base KF is still necessary in this latter reaction, since only a trace amount of the product is obtained without it.

2.4. Scope of the internal alkyne

Under our 'optimal' conditions, a wide variety of internal alkynes have been successfully employed in all cases studied so far. The reactions proceed in a very stereoselective manner. When symmetrical alkynes, such as diphenylacetylene or 4-octyne, are employed, only one pure stereoisomer is generated and the vinylic group and the aryl group from the arylboronic acid have been unambiguously determined by NOSEY experiments (see the [Supporting data](#)) to exist in a *cis*-configuration. Diaryl and more electron-rich dialkyl acetylenes have provided the desired 1,3-dienes in excellent yields (entries 26–28), as opposed to the generation of substantial amounts of multi-alkyne insertion products in the analogous coupling of aryl iodides and 4-octyne.⁸

Two isomers have generally been obtained with moderate to excellent regioselectivity when unsymmetrical alkynes are employed. The regiochemistry is primarily controlled by steric effects in all examples so far examined. The initial vinylic palladium intermediate usually adds the Pd moiety to the more hindered end of the triple bond, where the longer carbon–palladium bond is presumably more favorable energetically than the shorter carbon–carbon bond, that is, formed. Thus, the vinylic group generated from the vinylic halide generally adds to the less hindered end of the alkyne, while the aryl group from the arylboronic acid adds to the other end of the alkyne. Obviously, the greater the difference in the size of the two groups attached to the end of the alkyne, the better the regioselectivity is expected to be. Only modest selectivity was observed for 1-phenylpropyne, no matter what vinylic halide was employed (entries 29–31). The regioselectivity was improved greatly when using 1,4-diphenylbutadiyne (entry 32). Quite good regioselectivities were obtained for 1-phenyl-3,3-dimethyl-1-butyne (entry 33) and 4,4-dimethyl-2-butyne (entry 34). The relatively low yield from 4,4-dimethyl-2-butyne may in part be due to the fact that 4,4-dimethyl-2-butyne is relatively volatile (bp 80 °C) under our standard reaction conditions (100 °C). These results are consistent with our and others' previous work^{13,15} on the regiochemistry of palladium-catalyzed additions to alkynes.

Electronic effects also play an important role in the regiochemistry. The aryl group from the arylboronic acid prefers to add to the more electron-poor end of the alkyne, assuming steric effects are comparable. Therefore, surprisingly high 86:14 regioselectivity is observed when 1-(4-nitrophenyl)-1-hexyne is used as the alkyne (compare entry 35 with entry 29). In the absence of the nitro group, we get only a 60:40 ratio of regioisomeric dienes in a 44% yield. Substitution of the phenyl group with an electron-poor pyrimidine group has a similar effect (compare entries 36 and 29). When the steric and electronic effects work in opposition to each other, relatively poor regioselectivity is expected and indeed observed, as seen in examples involving a ketone- or ester-containing internal alkyne (entries 39–41). In these cases, steric effects apparently overrule electronic effects (presumably the phenyl group is more

sterically hindered than the ketone or ester groups, and the ketone and ester groups are more electron-poor than the phenyl group).

This process is tolerant of considerable functionality. Thus, ketone, ester, nitro, and alcohol (entries 37 and 38) groups are readily accommodated, providing the desired tetrasubstituted olefins in good to excellent yields.

The cross-coupling reactions of vinylic halides with terminal alkynes (either phenylacetylene or 1-heptyne) do not give clean products. The desired product; the product generated by carbopalladation of the alkyne by the vinylic halide, followed by cross-coupling of the vinylic palladium intermediate with the terminal alkyne in a Sonogashira-type reaction; along with side products formed by direct coupling of the vinylic halide and either the boronic acid or the terminal alkyne were all generated, making the reactions fairly messy.

It seemed obvious that the regiochemistry of the 1,3-dienes should be readily reversed if one were to start with an aryl iodide and cross-couple with a vinylic boronic acid. Thus, PhI, diphenylacetylene, and styrylboronic acid were allowed to react under conditions A. Unfortunately, only around a 5% yield of the desired product **3** was obtained and *trans*-1,2-diphenylethene was the primary product. We later found that reasonable yields of **3** and **5** can be obtained by employing 5 mol % of PdCl₂(PhCN)₂, 1 equiv of the aryl halide (0.25 mmol), 2 equiv of alkyne, 2 equiv of the vinylic boronic acid, 1 equiv of *n*-Bu₄NCl (TBAC), 50 equiv of H₂O, and 8 mL of DMF as the solvent at 100 °C in the presence of air for 12 h (Conditions C) (entries 42 and 43). Without TBAC, the yield of the reaction discussed in entry 42 dropped to 40%. H₂O (50 equiv) appears to be optimal, at least for this reaction.

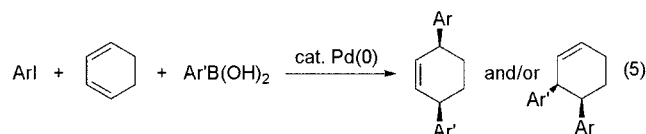
2.5. Mechanism

We propose the following mechanism for this three-component coupling reaction (Scheme 1): (1) reduction of Pd(II) to the actual catalyst Pd(0),¹⁶ (2) oxidative addition of the vinylic iodide to Pd(0) to produce a vinylic palladium intermediate **A**, (3) vinylpalladium coordination to the alkyne and subsequent *cis* insertion to form a new vinylpalladium intermediate **B**, (4) transmetalation with an 'ate' complex of the organoborane to form intermediate **C**, and, (5) reductive elimination of the product with regeneration of the Pd(0) catalyst. All steps are well precedented in organopalladium chemistry.¹⁷ While the majority of the reactions reported here are quite clean, in reactions affording much lower yields of dienes, side products consistent with this mechanism are observed. The potential side reactions are (1) immediate cross-coupling of intermediate **A** with the boronic acid to give simple Suzuki products, (2) multiple alkyne insertion to produce polyene products, (3)

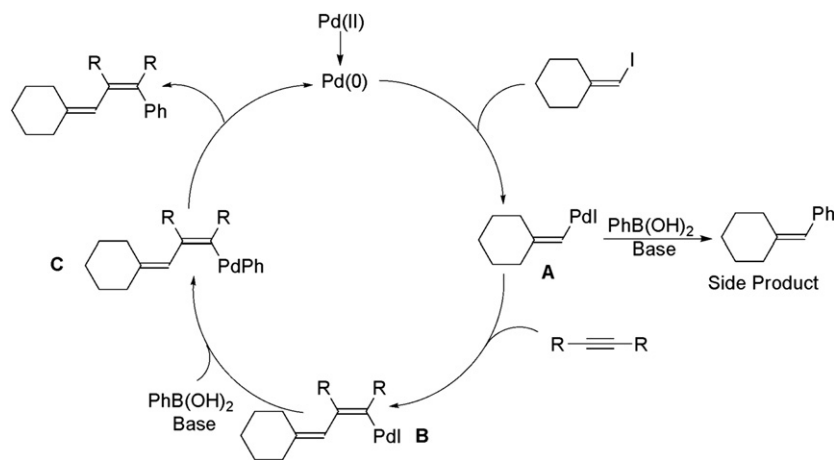
reduction of any of the organopalladium intermediates, and (4) dimerization of either the vinylic groups from the vinylic halide or the aryl groups from the arylboronic acid. All are well known organopalladium reactions,¹⁷ whose presence is likely to depend on steric and electronic effects, as well as the reagents available and the specific reaction conditions.

2.6. Cross-coupling of 1,3-cyclohexadiene

A synthetically interesting question is whether one can achieve the analogous coupling of aryl or vinylic halides with 1,3-dienes, followed by quenching of the resulting π -allylpalladium intermediate with a boronic acid (Eq. 5). Our success in the reactions of alkynes prompted us to investigate this intriguing reaction.



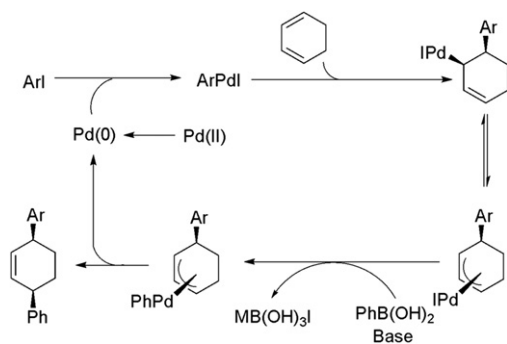
A brief optimization study indicated that a reaction involving 1 equiv of *p*-tolyl iodide, 4 equiv of 1,3-cyclohexadiene, 2 equiv of phenylboronic acid, 5 mol % of PdCl₂(PhCN)₂, 2 equiv of KF, and 5:1 DMF/H₂O as the solvent at 100 °C in the presence of air (Conditions D) provided the desired alkene in a 59% yield (Table 2, entry 44). The yield dropped to 50% when 2 equiv of K₂CO₃, instead of KF, were used as the base. The reaction became sluggish when water was not employed as a co-solvent. Based on known palladium chemistry, both 3,6-diarylcyclohexene and 3,4-diarylcyclohexene are possible products.^{17a} However, only one isomer was detected in our study through GC-MS and ¹H and ¹³C NMR experiments. The major product is believed to be the thermodynamically more stable *cis*-3,6-diarylcyclohexene as indicated by ¹H and ¹³C NMR spectral analysis. An interesting feature of this chemistry is that reactions employing electron-rich aryl iodides, such as 4-iodoaniline (entry 45), 4-iodophenol (entry 46) or 4-iodoanisole (entry 47) give the best yields and more importantly, free NH₂ and OH groups, which are known to be reactive nucleophiles in intramolecular reactions involving π -allylpalladium intermediates,¹⁸ remain untouched under our reaction conditions (entries 45 and 46). The higher yields obtained with these substrates presumably arise because the electron-releasing groups decrease the electrophilicity of the arylpalladium intermediate and thus suppress direct coupling with the boronic acid. In fact, when 4-iodoacetophenone was allowed to react with 1,3-cyclohexadiene and phenylboronic acid, none of the desired alkene product was observed (entry 48). Instead, 4-acetylbiphenyl was formed primarily. Unfortunately, the presence of



Scheme 1.

a group in the *ortho*-position of the aryl iodide appears to be a problem also, since the yield dropped significantly when *o*-tolyl iodide was employed as the aryl iodide (entry 49). On the other hand, the presence of a methyl group *ortho* to the boronic acid only slightly lowered the yield (entry 50). The yield also dropped when 4-chlorophenylboronic acid was employed (entry 51). We were pleased to find that a vinylic iodide **26** can be successfully employed in this process to generate a 1,4-skipped diene (entry 52). Unfortunately, other dienes, such as 1,3-cycloheptadiene and 2-methyl-1,3-butadiene failed to generate synthetically useful yields of the desired products. Direct cross-coupling of the aryl halide and arylboronic acid was the dominant process in the former reaction, while in the later case, the major product was the Heck product produced by β -hydride elimination of the π -allylpalladium intermediate as determined by GC–MS.

We believe that a mechanism similar to that of Scheme 1 is involved here (Scheme 2). The key steps are: (1) reduction of Pd(II) to the actual catalyst Pd(0),¹⁶ (2) oxidative addition of the aryl iodide to Pd(0) to produce an arylpalladium intermediate, (3) arylpalladium coordination to the 1,3-diene and subsequent *cis* insertion to form a π -allylpalladium intermediate, (4) transmetalation with an 'ate' complex of the organoborane to form a new π -allylpalladium intermediate, and (5) reductive elimination of the product with regeneration of the Pd(0) catalyst. All of these steps are well precedented in the organopalladium literature,¹⁷ although it is a bit surprising that reductive elimination of the olefin product is so regioselective. Presumably steric effects strongly favor the less hindered 1,4-addition product.



Scheme 2.

3. Conclusions

In summary, the palladium-catalyzed three-component coupling of vinylic halides, internal alkynes, and boron organometallics has been successfully achieved. The reaction is quite efficient, since it allows the selective construction of two carbon–carbon bonds in a single reaction from three simple starting materials. The reaction is insensitive to air and water. A wide range of vinylic halides, organoboron compounds, and internal alkynes with various functional groups can be employed in this process. The reaction involves *cis*-addition to the internal alkyne. The vinylic group from the vinylic iodide favors the less hindered or more electron-rich end of the alkyne, while the aryl group from the arylboronic acid adds to the other end of the alkyne. The generality of this process, combined with the good regio- and stereoselectivity, make this one-pot, two carbon–carbon bond forming process an attractive synthetic route to 1,3-dienes and 1,3,5-trienes bearing a tetrasubstituted carbon–carbon double bond. Finally, the analogous coupling of aryl or vinylic halides with 1,3-cyclohexadiene, followed by trapping of the π -allylpalladium intermediate with an arylboronic acid has also

been successful, providing a stereoselective method to prepare *cis*-3,6-disubstituted cyclohexenes.

4. Experimental section

4.1. General

The ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. (*E*)- β -Iodostyrene, iodomethylenecyclohexane, 1-iodo-4-phenylcyclohexene, bis[4-(ethoxycarbonyl)phenyl]acetylene, 3-iodocyclohex-2-en-1-ol, 3-iodo-5,5-dimethylcyclohex-2-enone, and compounds **3**, **10**, **12**, **14**, **16**, **23–25**, **32**, **34–37**, and **43** have been previously reported.⁹ (*E*)-1-Iodoct-1-ene,¹⁹ (*E*)-2-cyclohexylvinyl iodide,¹⁹ (*Z*)- β -iodostyrene,²⁰ 2-iodo-4,4-dimethyl-2-cyclohexen-1-ol,²¹ cyclohexylidene methyl triflate,²² and (bromomethylene)cyclohexane²³ were prepared according to previous literature procedures.

Conditions A: To a solution of vinylic halide (0.25 mmol), internal alkyne (0.50 mmol), and PdCl₂ (0.0125 mmol) in 5 mL of DMF was added 5 mL of a 2:1 DMF/H₂O solution of KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. **Conditions B:** A mixture of DMF (1.0 mL), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), LiCl (10.5 mg, 0.25 mmol), vinylic halide (0.50 mmol), internal alkyne (0.25 mmol), and tetraarylborate (0.50 mmol) was stirred in a reaction vial at room temperature for 3 min in the presence of air and then the vial was capped and heated to 100 °C with stirring for the specified time. **Conditions C:** To a solution of vinylic halide (0.25 mmol), internal alkyne (0.50 mmol), water (12.50 mmol), *n*-Bu₄NCl (0.25 mmol), and PdCl₂(PhCN)₂ (0.0125 mmol) in 8 mL of DMF was added KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. **Conditions D:** To a solution of aryl halide (0.25 mmol), 1,3-cyclohexadiene (1.00 mmol) and PdCl₂(PhCN)₂ (0.0125 mmol) in 10 mL of DMF/H₂O (5:1) was added KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. All reactions were monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (30 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (2 × 30 mL). The organic layers were combined, dried (MgSO₄), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column. The following 1,3-dienes, 1,3,5-trienes, and cyclohexenes have been prepared using these general procedures.

4.1.1. (*E*)-1,1,2-Triphenyl-1,3-decadiene (5). The reaction mixture was chromatographed using hexanes to afford 57 mg (62%) of the indicated compound as a light yellow oil: ¹H NMR (CDCl₃, 300 MHz) δ 0.88–0.93 (m, 3H), 1.24–1.32 (m, 8H), 2.02–2.08 (m, 2H), 5.39–5.49 (m, 1H), 6.43–6.48 (d, *J* = 15.6 Hz, 1H), 6.88–6.91 (m, 2H), 7.01–7.05 (m, 3H), 7.14–7.21 (m, 5H), 7.29–7.38 (m, 5H), 6.55–6.57 (m, 2H), 6.70–6.72 (d, *J* = 7.6 Hz, 1H), 6.95–6.98 (m, 2H), 7.04–7.45 (m, 14H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.2, 22.7, 28.9, 29.3, 31.8, 33.2, 125.9, 126.4, 127.0, 127.3, 127.7, 127.9, 131.1, 131.1, 131.5, 132.2, 136.2, 139.0, 139.8, 141.1, 142.8, 143.2; IR (CH₂Cl₂) 2935 cm⁻¹ HRMS *m/z* 366.2352 (calcd C₂₈H₃₀, 366.2348).

4.1.2. *cis*-3-(4-Aminophenyl)-6-phenylcyclohexene (51). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to

afford 55.4 mg (89%) of the indicated compound as an orange oil: ^1H NMR (CDCl_3 , 300 MHz) δ 1.65–1.71 (m, 2H), 1.87–1.96 (m, 2H), 3.26 (br s, 1H), 3.37–3.49 (m, 2H), 5.93 (s, 2H), 6.64–6.69 (m, 2H), 7.08–7.12 (m, 2H), 7.19–7.31 (m, 5H); ^{13}C NMR (CDCl_3) δ 29.5, 29.8, 40.5, 41.5, 115.5, 126.3, 128.2, 128.6, 129.0, 131.0, 131.9, 136.3, 144.7, 146.4; IR (CH_2Cl_2) 3372, 2934, 2860, 1624 cm^{-1} ; HRMS m/z 249.1523 (calcd $\text{C}_{18}\text{H}_{19}\text{N}$, 249.1518).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.03.119.

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