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Synthesis of Highly Substituted 1,3-Dienes and 1,3,5-Trienes by the Palladium-Catalyzed Coupling of Vinylic Halides, Internal Alkynes, and Organoboranes

Xiaoxia Zhang and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

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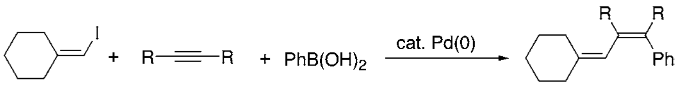
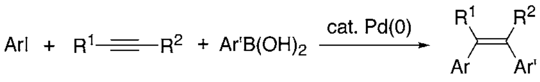
ABSTRACT



Highly substituted 1,3-dienes and trienes have been prepared in good to excellent yields by the palladium-catalyzed coupling of vinylic halides, internal alkynes, and organoboranes.

1,3-Dienes are valuable products or intermediates in organic chemistry.[1] While there are numerous methods presently available to prepare di- or trisubstituted carbon−carbon double bonds in 1,3-dienes, regio- and stereospecific methods to prepare more highly substituted dienes, especially those bearing tetrasubstituted double bonds, are quite limited.[2]

The propensity of unsaturated compounds, such as alkenes, allenes, and alkynes, to undergo insertion into carbon−metal bonds makes these substrates some of the most useful for transition-metal-catalyzed organic transformations.[3] Organoboronic acids and borates are widely used in the palladium-catalyzed Suzuki cross-coupling with organic halides, providing a very efficient route for carbon−carbon bond formation.[4] In previous work, we reported 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 1).[5]



(1)

The ability to achieve such sequential ternary cross-coupling[6] is highly attractive, since it allows the rapid, efficient, and selective construction of two carbon−carbon bonds in a single reaction. Grigg and co-workers have synthesized substituted 1,3-dienes through the *intramolecular* reaction of an aromatic halide with an internal alkyne, followed by cross-coupling with an external vinylic catecholborane.[7] We wish to report that the one-pot, *intermo-*

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[1] (a) Rappoport, Z. *The Chemistry of Dienes and Polyenes*; John Wiley & Sons: Chichester, 1997; Vol. 1. (b) Rappoport, Z. *The Chemistry of Dienes and Polyenes*; John Wiley & Sons: Chichester, 2001; Vol. 2.

[2] (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999; Chapter 2. (b) Vasil’ev, A. A.; Sterebryakov, E. P. *Russ. Chem. Rev.* **2001**, *70*, 735.

[3] (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. T. *Chem. Rev.* **1996**, *96*, 635.

[4] For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2. (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

[5] Zhou, C. X.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

[6] For examples of the Pd-catalyzed tandem coupling of organic halides, unsaturated compounds and organoboranes, see: (a) Yang, F. Y.; Wu, M. Y.; Cheng, C. H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (b) Huang, T. H.; Chang, H. M.; Wu, M. Y.; Cheng, C. H. *J. Org. Chem.* **2002**, *67*, 99. (c) Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 4317. (d) Shaulis, K. M.; Hoskin, B. L.; Townsend, J. R.; Goodson, F. E.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2002**, *67*, 5860.

[7] (a) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803. (b) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135.

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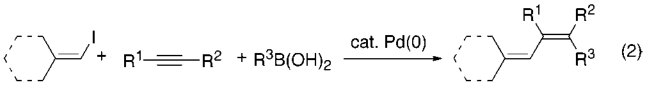
lecular palladium-catalyzed coupling of vinylic iodides, internal alkynes, and boron organometallics offers an efficient, direct route to a number of highly substituted 1,3-dienes (eq 2).



Our initial studies of this process focused on developing an optimum set of reaction conditions for this three-component reaction. The key to the success of the reaction lies in the choice of solvent and base, so as to avoid direct cross-coupling between the vinylic halide and the organoboron compound or multiple alkyne insertion processes. The effect of various reaction parameters (base, phosphine, chloride source, stoichiometry, solvent, concentration, and temperature) on the yield of 1,3-dienes was studied. When tetraarylborates are employed as the organometallics, the optimal reaction conditions thus far achieved (conditions A in Table 1) utilize 2 equiv of the vinylic halide, 1 equiv of the internal alkyne, 2 equiv of borate, 5 mol % of $Pd(OAc)_2$, and 1 equiv of LiCl in DMF at 100 °C in the presence of air. The presence of phosphine ligands inhibits the catalytic reaction. Lower reaction temperatures extend the reaction time without improving the yield of the reaction.

The three-component assembly using various internal alkynes, tetraarylborates and vinylic halide **1** under conditions A affords the desired 1,3-dienes in good yields (entries 1−3, Table 1). For example, the reaction of diphenylacetylene and sodium tetraphenylborate affords the desired product **2** in a 71% yield. The more electron rich tetrathiophenylborate affords product **3** in an 80% yield. It is noteworthy that for the unsymmetrical alkyne 1-(4-nitrophenyl)-1-hexyne, one major stereo- and regioisomer was isolated in a 62% yield (entry 3). In the absence of the nitro group, we get a 1.5:1 ratio of regioisomeric dienes in a 44% yield. The regioselectivity is governed by both steric and electronic factors with the larger and more electron-poor substituent on the triple bond ending up at the 1-position of the 1,3-diene. This regioselectivity is consistent with the regioselectivity observed in other palladium-catalyzed insertions involving internal alkynes.[8]

We have also investigated reactions with boronic acids, since functionalized boronic acids are more readily available than organoborates. However, when the optimum conditions used for tetraarylborates (conditions A) were employed in the cross-coupling of vinylic halide **5**, diphenylacetylene, and phenylboronic acid, the desired diene was obtained in only a trace amount. “Optimal” conditions B have been developed employing 1 equiv of a vinylic halide, 2 equiv of internal alkyne, 2 equiv of arylboronic acid, 5 mol % of $PdCl_2$, 2 equiv of KF, and 5:1 DMF−H_2O as the solvent at 100 °C in the presence of air. This procedure affords an 87% yield of **6** (entry 4). The use of DMF−H_2O as the solvent is crucial for the success of reactions involving dialkyl and alkyl aryl alkynes. Changing the base from KF to KOAc, K_2CO_3, K_3PO_4, or organic amine bases failed to improve the yields of the desired products.

The optimized conditions B were subsequently examined in reactions of vinylic halide **5**, diphenylacetylene and various arylboronic acids. 4-Methoxyphenylboronic acid afforded a 93% yield of the desired diene, compared to the 56% yield obtained from 3-nitrophenylboronic acid (compare entries 5 and 6). Thus, electron-rich arylboronic acids give better results in this process. We assume that this is due to more rapid transmetalation of the dienylpalladium intermediate with the more electron-rich arylboronic acid, which suppresses side reactions, such as further alkyne insertion (see the latter mechanistic discussion). The relatively hindered *o*-tolylboronic acid also gives the corresponding product in a high yield, 82% (entry 7). Thus, steric effects in the reaction with the arylboronic acid appear to be minimal.

As shown in entries 8 and 9, the reaction conditions are very effective in the reaction of a dialkyl alkyne and a diester-substituted diarylacetylene with vinylic halides **5** and **11** respectively. Interestingly, the reactions of the more sterically hindered vinylic halide **14** afford the corresponding 1,3-dienes in good yields when employing either diaryl (entry 11) or dialkyl alkynes (entry 12). However, the cross-coupling reactions of these halides with terminal alkynes do not appear to give clean products.

Unfortunately, the reaction of 3-iodo-5,5-dimethylcyclohex-2-enone (**17**) and diphenylacetylene affords mostly product in which the vinylic halide and arylboronic acid undergo direct cross-coupling without insertion of the alkyne (entry 13). None of the desired 1,3-diene was observed. Obviously, an electron-withdrawing group on the β-position of the vinylic halide facilitates direct nucleophilic transmetalation of the boronic acid with the organopalladium(II) intermediate **A**, rather than alkyne insertion, resulting in monoene product.[4c] On the other hand, the allylic alcohol-containing vinylic halide **19** reacts with diphenylacetylene under our standard reaction conditions to give the desired diene **20** in a 41% yield, which should be easily converted to the corresponding ketone. While vinylic bromides appear to react under our usual reaction conditions, these reactions are very slow.

The nature of the boronic acid was expanded to alkenyl variants. Thus, vinylic iodide **11** was allowed to react with 2-butyne-1,4-diol and styrylboronic acid to afford a 57% yield of triene **13** (entry 10). This protocol thus allows for the synthesis of multi-substituted trienes in one pot. Alternatively, the sequential reaction of an aryl halide, an internal alkyne, and a vinylic boronic acid also affords a multi-substituted 1,3-diene as illustrated by the reaction of iodobenzene (**21**), diphenylacetylene and styrylboronic acid (entry 15), although decent yields in this case have only been obtained by employing different reaction conditions (Table 1).

We propose the following mechanism, which involves the following key steps for this three-component coupling reaction (Scheme 1): (1) reduction of Pd(II) to the actual catalyst Pd(0), (2) oxidative addition of the vinylic iodide

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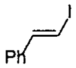
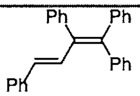
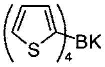
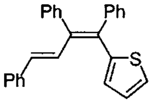
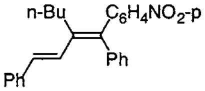
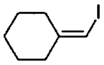
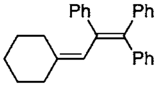
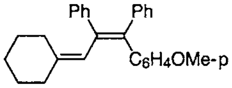
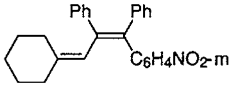
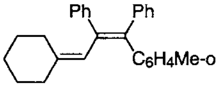
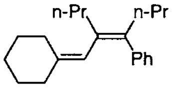
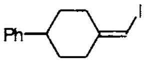
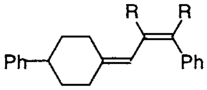
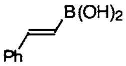
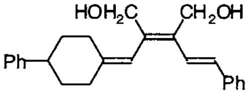
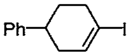
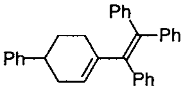
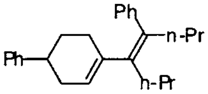
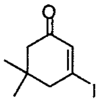
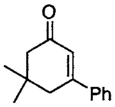
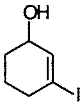
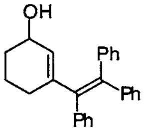
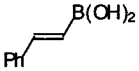
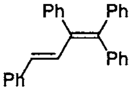
[8] (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579. (c) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643.

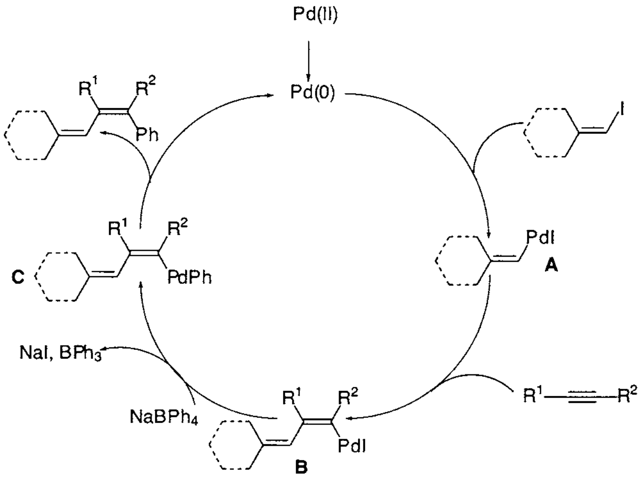
Table 1. Palladium-Catalyzed Three-Component Coupling of Vinylic Halides, Internal Alkynes, and Organoboranes[a]

entry	vinylic halide		alkyne	organoborane	cond., time (h)	product		% yield[b]
1		**1**	Ph—≡—Ph	$NaBPh_4$	A, 12		**2**	71[c]
2					A, 12		**3**	80
3			n-Bu—≡—$C_6H_4NO_2$-p	$NaBPh_4$	A, 12		**4**	62
4		**5**	Ph—≡—Ph	$PhB(OH)_2$	B, 2		**6**	87
5				p-$MeOC_6H_4B(OH)_2$	B, 2		**7**	93
6				m-$O_2NC_6H_4B(OH)_2$	B, 2		**8**	56
7				o-$MeC_6H_4B(OH)_2$	B, 2		**9**	82
8			n-Pr—≡—n-Pr	$PhB(OH)_2$	B, 2		**10**	85
9		**11**	R—≡—R R = $C_6H_4CO_2Et$-p		B, 2	 R = $C_6H_4CO_2Et$-p	**12**	68
10			HOH_2C—≡—CH_2OH		B[d], 2		**13**	57
11		**14**	Ph—≡—Ph		B, 2		**15**	78
12			n-Pr—≡—n-Pr		B, 2		**16**	63
13		**17**	Ph—≡—Ph	$PhB(OH)_2$	B, 2		**18**	90
14		**19**			B, 2		**20**	41
15	PhI	**21**			C[e], 4		**2**	58

[a] All reactions were carried out under the optimal conditions reported in the text. [b] Isolated yield. [c] Yield determined by GC. [d] 6 equiv of KF was employed. [e] Conditions C: 5 mol % of $PdCl_2(PhCN)_2$, 1 equiv of aryl halide, 2 equiv of alkyne, 2 equiv of vinyl boronic acid, 1 equiv of n-Bu_4NCl, 50 equiv of H_2O, and 8 mL of DMF as the solvent at 100 °C in the presence of air for the indicated time.

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**,[9] (4) transmetalation with an “ate” complex[4a,10] of the orga-

Scheme 1



noborane 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.[11] 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 (particularly products from direct Suzuki cross-coupling of the vinylic halides and organoboranes).

In conclusion, the palladium-catalyzed three-component coupling of vinylic halides, internal alkynes and boron organometallics has been successfully achieved. A wide range of vinylic halides, organoboron compounds, and internal alkynes with various functional groups may be used in this process. This generality, 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 trienes bearing a tetrasubstituted carbon−carbon double bond.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc., for donating the palladium acetate. The boronic acids were contributed by Frontier Scientific, Inc.

Supporting Information Available: General experimental procedures and spectral data for the dienes listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The *cis*-alkyne insertion has been proven by the structures of products which were determined by NOESY NMR experiments.

(10) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(11) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, 1995. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vols. 1 and 2.