

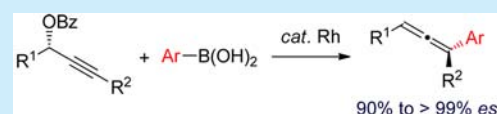
## Rh-Catalyzed Stereospecific Synthesis of Allenes from Propargylic Benzoates and Arylboronic Acids

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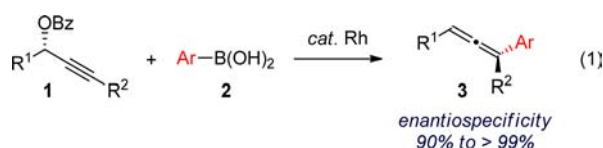
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## Supporting Information

**ABSTRACT:** An enantiospecific approach to the synthesis of optically active, trisubstituted allen es from chiral propargylic benzoates and arylboronic acids has been developed. The transformation is catalyzed by a Rh–(P,olefin) complex formed *in situ* from  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$  and a readily available phosphoramidite ligand. The method furnishes an assortment of diverse allen es in high yields and excellent enantiospecificity under mild conditions.



Allen es are an important class of compounds due to their unique reactivity and their use as building blocks in complex molecule synthesis.<sup>1</sup> The transition-metal-catalyzed  $\text{S}_{\text{N}}2'$  reaction between propargyl alcohol derivatives and organometallic reagents constitutes one of the most important approaches for the preparation of optically active allen es.<sup>2</sup> Herein, we disclose a preparation of enantioenriched allen es from chiral propargylic benzoates and arylboronic acids. The reaction employs a Rh-catalyst formed *in situ* from a simple, achiral phosphoramidite ligand and commercially available  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ . This method allows access to chiral, trisubstituted allen es in high enantiomeric excess from the corresponding propargylic alcohols (eq 1). As such, the Rh-



catalyzed synthesis of chiral allen es from widely available boronic acids is complementary to related, previously reported Cu- and Pd-catalyzed reactions.<sup>3</sup> Furthermore, to the best of our knowledge, a transition-metal-catalyzed, enantiospecific synthesis of chiral, trisubstituted allen es from propargyl alcohol derivatives and arylboronic acids has not been reported.

The traditional approaches to allen es from propargyl electrophiles prescribe the use of stoichiometric amounts of reactive organometallic reagents as coupling partners, derived from In(III), Zn(II), Mg(II), and Cu(I). More recently, alkyl-, vinyl-, and arylboron reagents have been used in the preparation of chiral allen es from enantioenriched propargylic alcohol derivatives under Pd- or Cu-catalysis.<sup>3</sup> The sole example involving Rh-catalysis employs alkynyl epoxides as electrophiles and arylboronic acids, in a reaction displaying high regio- and stereoselectivity to give allen es.<sup>4,5</sup> However, the requisite starting materials, namely optically active alkynyl epoxides, are not readily accessible, requiring a multistep sequence of reactions for their synthesis. Enantioenriched propargylic alcohols on the contrary may be readily accessible

from the asymmetric addition of terminal alkynes to aldehydes<sup>6</sup> or the reduction of  $\alpha,\beta$ -alkynyl ketones by the methods described by Corey, Noyori, or Midland.<sup>7</sup>

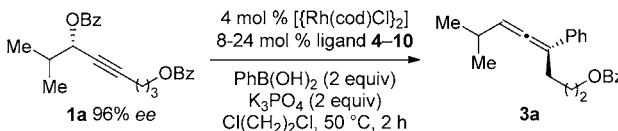
Our investigations commenced by studying the Rh-catalyzed reaction between propargylic carbonates and phenylboronic acid (2a) as test substrates. In the presence of  $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ , ligand 4 (1:1 ligand/Rh), and  $\text{Cs}_2\text{CO}_3$  in 1,4-dioxane/water, the reagents were observed to undergo reaction to furnish the corresponding allene. However, under these conditions, no chirality transfer was observed, leading to product formation as a racemate. After extensive experimentation, we observed that variation of the solvent, ligand (e.g., 4–10), ligand-to-metal ratio, and base had a significant impact on the yield and enantiospecificity of the process. Propargylic benzoates were found to give comparable results as carbonates (see Supporting Information for an example) while 4- $\text{NO}_2$ -benzoates gave the products with lower selectivity. Accordingly, when the reaction between propargylic benzoate 1a (96% ee) and phenylboronic acid (2a) was conducted in 1,2-dichloroethane as solvent with 2:1 4/Rh(I) and  $\text{K}_3\text{PO}_4$  as base, full conversion to adduct 3a in 98% es was observed (Table 1, entry 1). Following a screening of a number of other ligands (5–10), phosphine-olefin phosphoramidite 4 was identified as the optimal ligand (see Supporting Information for details).<sup>8</sup>

With the optimal reaction conditions identified, the scope of the method was examined (Scheme 1). Propargylic benzoates (ee  $\geq$  96%) 1a–j were prepared by the asymmetric addition of terminal alkynes to aldehydes and subsequent benzylation.<sup>6a</sup> Benzoate 1k was accessed through CBS-reduction of the corresponding  $\alpha,\beta$ -ynone.<sup>7d</sup> Reaction of these benzoates with various arylboronic acids 2 gave allen es 3 in good to excellent yields, and the observed selectivities were high ( $\geq$ 90% es) in all cases. The propargylic electrophiles can be substituted with a protected amine (3f–3h), ester (3a–3e), or alkyl bromide (3k). Electron-rich (3c, 3d, 3h) and electron-poor (3f, 3i, 3j) arylboronic acids may serve as coupling partners. *Ortho*-

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Table 1. Selected Ligand Screening Studies



entry	ligand	conversion (%) <sup>a</sup>	es (%) <sup>b</sup>
1	4	>95	98
2	5	46	98
3	(BnO) <sub>2</sub> PN(iPr) <sub>2</sub> (6)	<5	n.d. <sup>c</sup>
4	7	>95	89
5	DPPF (8)	>95	91
6	9	>95	94
7	P(OMe) <sub>3</sub> (10)	61	83

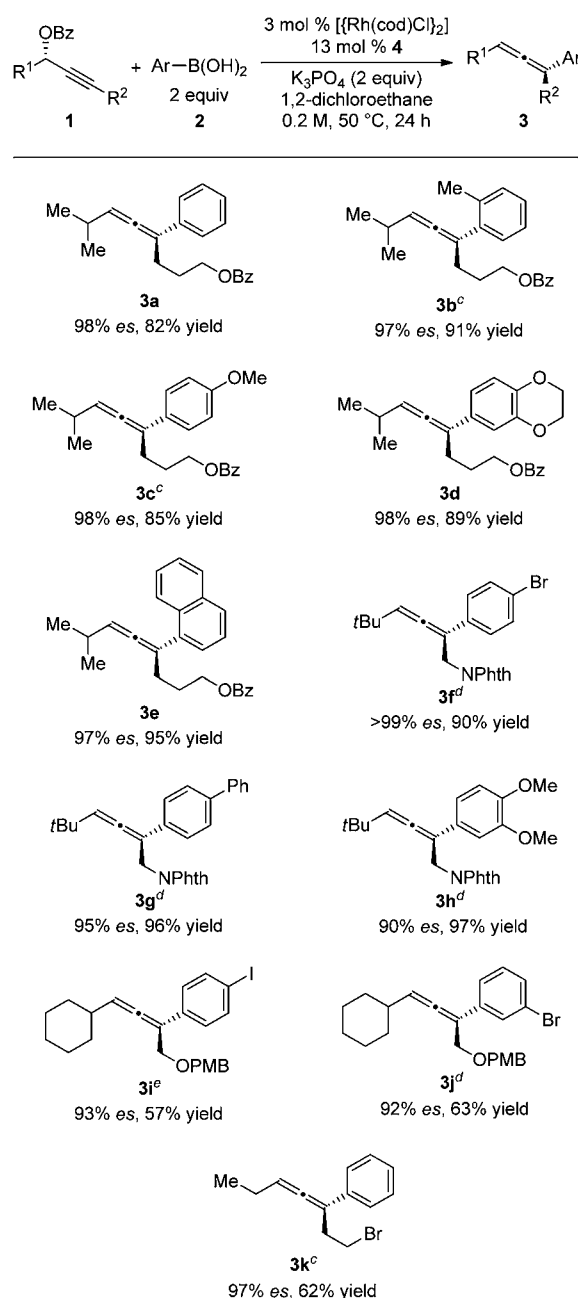
<sup>a</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.<sup>b</sup>Determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. <sup>c</sup>Not determined.

substitution of the boronic acid was well tolerated (3b, 3e). Although most substrates gave full conversion and good to excellent yields using readily available [ $\text{Rh}(\text{cod})\text{Cl}$ ]<sub>2</sub> under the conditions described above, we have found that the addition of water generally led to an increase of the reaction rate while the selectivity was slightly lowered. For example, full conversion (96% yield) and 95% *es* were observed in the synthesis of 3g when 10 equiv of water were added to the reaction mixture. In the absence of added water, an allene adduct was isolated in 79% yield and 99% *es*. We also noted that the use of [ $\text{Rh}(\text{cod})\text{OH}$ ]<sub>2</sub> resulted in higher conversions in certain cases.

In general, the substrates can be substituted with linear, branched secondary or tertiary alkyl groups (R<sup>1</sup>) in  $\alpha$ -position to the propargylic benzoate. The reaction is slower with increasing size of the substituent on the alkyne distal to the benzoate (R<sup>2</sup>). The starting materials were cleanly recovered for substrates with Me<sub>3</sub>Si-substituted alkynes (R<sup>2</sup>). As a limitation, strongly electron-poor arylboronic acids as well as vinyl- and alkylboronic acids are not suitable coupling partners at the current level of development. Preliminary experiments revealed that the use of terminal alkynes in the reaction gave a complex mixture of products, from which none could be identified as being allenes.<sup>9,10</sup>

The structures of three allene products (3f–3h) were confirmed by X-ray crystallographic analysis, and the absolute configuration for 3f was established accordingly.<sup>11</sup> On the basis of this configurational assignment, some insight can be gained and a mechanism can be proposed. Hence, the reaction likely proceeds through regioselective arylrhodation of the alkyne to give an organorhodium intermediate (Scheme 2: 12 + 1  $\rightarrow$  13) followed by a selective *syn*-elimination to yield the observed allene.<sup>4a,5a,12</sup> An alternative mechanism proceeding through an allenyl-Rh intermediate cannot be excluded.<sup>3a–c</sup> Interestingly, no products from direct S<sub>N</sub>2 substitution were observed.

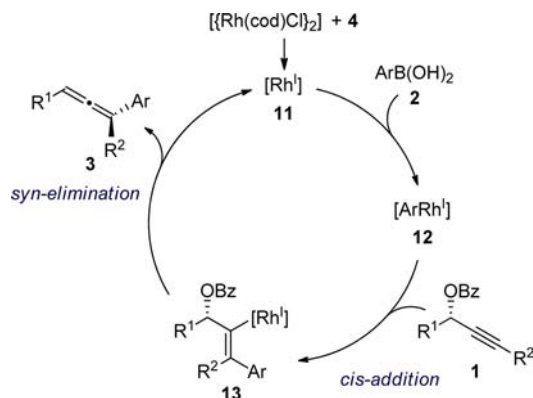
In conclusion, we have disclosed the first example of a Rh-catalyzed, stereoselective synthesis of allenes from chiral propargylic alcohol derivatives and arylboronic acids. This method furnishes structurally diverse trisubstituted allenes in

Scheme 1. Scope of the Rh-Catalyzed Synthesis of Trisubstituted Allenes<sup>a,b</sup>

<sup>a</sup>Yields refer to isolated products after purification by chromatography on silica gel. <sup>b</sup>Enantiomeric excesses were determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. <sup>c</sup>Reaction conducted at 40 °C for 12 h. <sup>d</sup>10 equiv of H<sub>2</sub>O were added. <sup>e</sup>10 equiv of H<sub>2</sub>O were added, and [ $\text{Rh}(\text{cod})\text{OH}$ ]<sub>2</sub> (3 mol %) was used.

good yields and with high stereoselectivity ( $\geq 90\%$  *es*). The chiral propargylic alcohol derivatives employed are readily accessible through enantioselective addition of alkynes to aliphatic aldehydes or asymmetric ketone reductions. Thus, the method allows the synthesis of enantioenriched allenes in a convergent and stereoselective manner from simple precursors under mild conditions and without the use of sensitive organometallic reagents.

**Scheme 2. Mechanistic Proposal Accounting for the Observed Absolute Configuration through *cis*-Addition and *syn*-Elimination<sup>5a</sup>**



## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00793.

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

X-ray data for compound 3f (CIF)

X-ray data for compound 3h (CIF)

X-ray data for compound 3g (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Zimmer, R.; Dinesh, C. U.; Nandan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (g) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074. (h) Grillet, F.; Brummond, K. M. *J. Org. Chem.* **2013**, *78*, 3737. (i) Neff, R. K.; Frantz, D. E. *Tetrahedron* **2015**, *71*, 7. (j) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. *Nat. Commun.* **2015**, *6*, 7946.
- (2) For selected reviews on the synthesis of allenes, see: (a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 2007, 795. (c) Yu, S.; Ma, S. *Chem. Commun.* **2011**, 47, 5384. (d) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014**, *4*, 519. (e) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 1210. For a recent review covering the transition-metal-catalyzed, enantioselective and enantiospecific synthesis of allenes from organometallic reagents, see: (f) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587.
- (3) For Pd-catalyzed, stereoselective synthesis of allenes from propargylic alcohol derivatives and aryl- or alkenylboron compounds,

see: (a) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573. (b) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563. (c) Yoshida, M.; Okada, T.; Shishido, K. *Tetrahedron* **2007**, *63*, 6996. For Cu-catalyzed, stereoselective preparation of allenes from propargylic alcohol derivatives and boron nucleophiles, see: (d) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774. (e) Yang, M.; Yokokawa, N.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2012**, *14*, 816. For the synthesis of allenylsilanes, see: (f) Vyas, D. J.; Hazra, C. K.; Oestreich, M. *Org. Lett.* **2011**, *13*, 4462. (g) Hazra, C. K.; Oestreich, M. *Org. Lett.* **2012**, *14*, 4010. (h) Yokobori, U.; Ohmiya, H.; Sawamura, M. *Organometallics* **2012**, *31*, 7909. For the synthesis of alkyl substituted allenes utilizing alkylboron reagents, see: (i) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011**, *13*, 6312. (j) Uehling, M. R.; Marionni, S. T.; Lalic, G. *Org. Lett.* **2012**, *14*, 362.

(4) (a) Miura, T.; Shimada, M.; Ku, S.-Y.; Tamai, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101. For related studies to this work, see: (b) Miura, T.; Shimada, M.; de Mendoza, P.; Deutsch, C.; Krause, N.; Murakami, M. *J. Org. Chem.* **2009**, *74*, 6050. (c) Yoshida, M.; Hayashi, M.; Matsuda, K.; Shishido, K. *Heterocycles* **2009**, *77*, 193. For the Rh-catalyzed, stereospecific synthesis of allenylsilanes from propargylic carbonates, see: (d) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618. (e) For a Rh-catalyzed synthesis of tetrasubstituted, chiral allenes, see ref 1j.

(5) For an example where the stereoselectivity was found to be low with propargylic alcohol derivatives under Rh-catalysis, see: (a) Murakami, M.; Igawa, H. *Helv. Chim. Acta* **2002**, *85*, 4182. For a selected example under Fe-catalysis, see: (b) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355.

(6) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (d) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8. For a selected review, see: (e) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(7) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(8) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. For the use of a phosphine olefin phosphoramidite ligand in a Rh-catalyzed enantioselective intramolecular hydroacylation reaction, see: (b) Hoffman, T. J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10670.

(9) For a Rh-catalyzed propargylic amination reaction of terminal alkynes, see: Evans, P. A.; Lawler, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4970.

(10) For selected, recent work employing allenes as starting materials under Rh<sup>I</sup>-catalysis, see: (a) Kawamoto, T.; Hirabayashi, S.; Guo, X.-X.; Nishimura, T.; Hayashi, T. *Chem. Commun.* **2009**, 3528. (b) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746. (c) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162. (e) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268. (f) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862. (g) Li, C.; Kahny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780. (h) Pritzius, A. B.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 3121. (i) Haydl, A. M.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 7149. (j) See also ref 1h and references therein.

(11) CCDC 1437268 (3f), 1446561 (3g), and 1437269 (3h) contain the supplementary crystallographic data for this publication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

(12) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876.