

Published in final edited form as:

Org Lett. 2009 September 17; 11(18): 4092–4095. doi:10.1021/ol901566e.

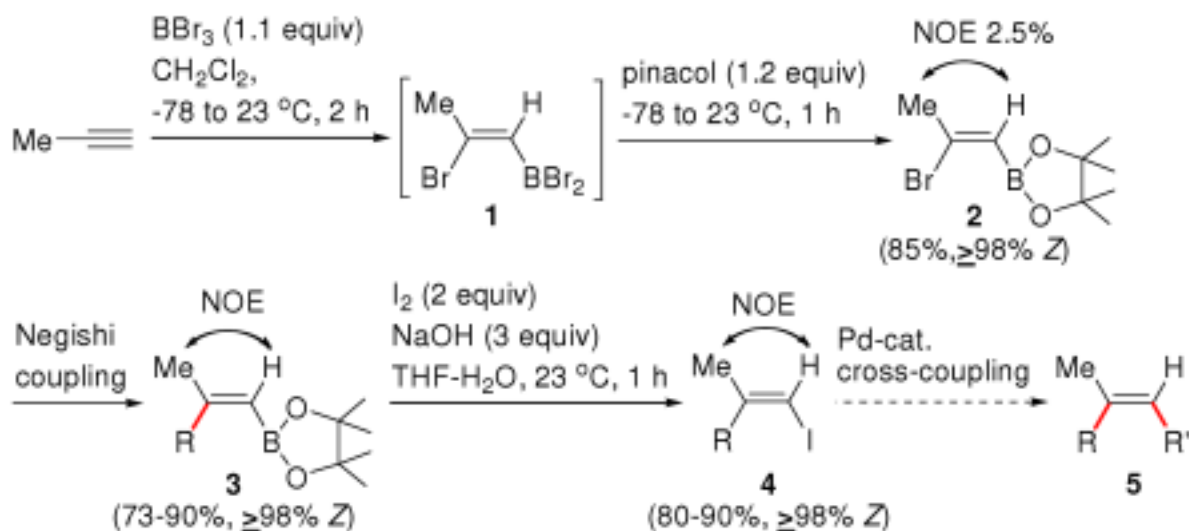
## Highly Regio- and Stereoselective Synthesis of (*Z*)-Trisubstituted Alkenes via Propyne Bromoboration and Tandem Pd-Catalyzed Cross-Coupling

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### Abstract



Contrary to all previous reports, bromoboration of propyne with  $\text{BBr}_3$  proceeds in  $\geq 98\%$  *syn*-selectivity to produce (*Z*)-2-bromo-1-propenyldibromoborane (1). Although 1 is readily prone to stereoisomerization, it can be converted to the pinacolboronate (2) of  $\geq 98\%$  isomeric purity by treatment with pinacol, which may then be subjected to Negishi coupling to give trisubstituted (*Z*)-alkenylpinacolboronates (3) containing various R groups in 73–90% yields. Iodinolysis of 3 affords alkenyl iodides (4) in 80–90% yields. All alkenes isolated and identified are  $\geq 98\%$  *Z*.

Zr-Catalyzed carboalumination of alkynes,<sup>1</sup> especially methylalumination (ZMA, hereafter), has been widely used for the synthesis of *E*-trisubstituted alkenes, especially those of the terpenoid origin.<sup>2</sup> Although the corresponding methylcupration of alkynes has not been well developed, alkylcupration<sup>3</sup> of propyne can provide a potentially attractive route to (*Z*)-trisubstituted alkenes of terpenoid origin with a Me branch. One general deficiency common to these alkyne carbometalation reactions is that their current scope is practically limited to

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 Supporting Information Available Experimental details and representative  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

those cases where alkylmetals including allyl- and benzylmetals are used. Haloboration reported in 1964 by Lappert<sup>4</sup> is a rare example of halometalation which is thermodynamically favorable due mainly to the relatively high electronegativity of boron. Subsequent Pd-catalyzed cross-coupling would provide a potentially selective route to trisubstituted alkenes of unprecedentedly wide scope. Although this was realized first by Suzuki in 1988 with a Pd-catalyzed tandem Negishi–Suzuki coupling process<sup>5</sup> and more recently by Wang<sup>6</sup> with a double Negishi coupling process, these previous studies collectively fell short of the above-stated promise. Notably, in the single most desirable case of propyne haloboration for the selective synthesis of (*Z*)-alkene-containing terpenoids, all reported stereoselectivity values were  $\leq 89\%$ .<sup>6c,8,9</sup> Secondly, although haloboration itself appears to proceed satisfactorily not only with alkyl-substituted alkynes but also with other types of alkynes substituted with Ph and cyclohexenyl,<sup>8a,9a,10</sup> those subjected to Pd-catalyzed cross-coupling have been strictly limited to the cases of alkyl-substituted alkynes.<sup>5–7</sup>

We herein report that, contrary to the previous claim,<sup>8b</sup> *bromoboration of propyne with BBr<sub>3</sub> does proceed in  $\geq 98\%$  syn-selectivity to produce (*Z*)-2-bromo-1-propenyldibromoborane (1) and that, although 1 is indeed highly prone to stereoisomerization under a variety of conditions, it can be converted to the corresponding cyclic boronate (2) of  $\geq 98\%$  stereoisomeric purity by its treatment with pinacol at room temperature.* Compound 2 is stable and can be stored in air at 23 °C for days without any changes by NMR analyses. All other alcohols including methanol, ethanol, and isopropanol, as well as some amines and *S*-based nucleophiles tested so far have led to stereoisomerization occurring to unacceptable extents ( $>10\%$ ). As expected, the Pd-catalyzed cross-coupling of 2 with a wide range of organozincs (Negishi coupling)<sup>11</sup> including alkyl, allyl, benzyl, alkenyl, aryl, and alkynyl groups proceed to give 3 in high yields with full retention ( $\geq 98\%$ ) of stereochemistry (Table 1). It should be noted that those obtained with the use of organozincs containing alkenyl, aryl, and alkynyl groups may not be readily accessible via known alkyne carbometalation, such as those mentioned above.<sup>1–3</sup> Our brief survey of the metal counterions (M) of the organometallic reagent (RM) for the substitution of Br with a carbon groups (R) has indicated Zn is indeed the most satisfactory metal counterion, although In and Zr are also satisfactory. Thus, for example, 3x (R = (*E*)-*n*-HexCH=CH), prepared in 96% yield by using (*E*)-*n*-HexCH=CHZnBr (Entry 10), was obtained by the use of (*E*)-*n*-HexCH=CHM in lower NMR yields of  $\leq 2\%$  (M = Mg or Al), 82%, (M = In), 18% (M = Cu), and 73% (M = Zr).

To complete the synthesis of trisubstituted alkenes free of both Br and B, the most obvious and straightforward route would be to resort to the Suzuki coupling<sup>12</sup> of 3. However, direct Pd-catalyzed Suzuki coupling of (*Z*)- $\beta$ -substituted alkenylboranes with alkenyl and alkynyl halides run under the previously reported conditions<sup>5</sup> has tended to give the desired products in relatively low ( $<50$ – $60\%$ ) yields.<sup>5,13</sup> Pd-catalyzed reactions of alkenylboranes with alkyl and cyanogen halides tend to be less satisfactory than those of the corresponding alkenyl iodides with alkylmetals and metal cyanides.<sup>11</sup> As shown in Table 1, alkenyl iodides (4) required in the latter protocol are obtained by treatment of 3 with I<sub>2</sub> (2 equiv) and NaOH (3 equiv) in THF and H<sub>2</sub>O at 23 °C<sup>14</sup> in uniformly high yields of 80–90% with full ( $\geq 98\%$ ) retention of isomeric purity of 3. It should be emphasized that the propyne bromoboration–Negishi coupling protocol summarized in Table 1 represents an efficient and highly ( $\geq 98\%$ ) selective route to (*Z*)-2-methyl-1-alkenylboranes (3) and the corresponding iodides (4)<sup>15</sup> of unprecedentedly broad potential scope, and that none of the examples of 3 or 4 in Table 1 have previously been prepared in a highly selective ( $\geq 98\%$ ) manner via propyne haloboration.

Some of the alkenyl iodides (4) have been previously prepared via more circuitous routes in considerably lower yields. Thus, for example, 4ix, obtained in three steps from propyne in 60% overall yield and  $\geq 98\%$  *Z* selectively, was previously prepared from 3-butyn-1-ol also in three steps but only 41% yield and *ca.* 95–97% *Z* selectivity<sup>16</sup> (Equation 1 of Scheme 1). It should

be remembered that treatment of **4ix** with just one equiv of *n*-BuLi followed by addition of geranyl bromide of  $\geq 98\%$  isomeric purity furnished (3*Z*, 6*E*)- $\alpha$ -farnesene (**6**) of  $\geq 98\%$  isomeric purity in 80% yield without using any catalyst.<sup>16</sup> We recently reported the preparation of a key intermediate **7** for the synthesis of the sidechain of mycolactone A<sup>17,18</sup> from propargyl alcohol in 42% yield over six steps and  $\geq 98\%$  selectivity.<sup>17</sup> The same compound **7** can now be synthesized from propyne and propargyl alcohol in mere two steps in 62% overall yield (Equation 2 of Scheme 1). Finally, treatment of **2** with TBSC $\equiv$ CZnBr in the presence of 0.1 mol % of Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub> and the with I<sub>2</sub> and NaOH gave iodoenone **4xviii** ( $\geq 98\%$  *Z*) in 79% yield. Pd-catalyzed cyanation<sup>19</sup> of **4xviii** with Zn(CN)<sub>2</sub> in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> followed by desilylation with TBAF provided **9** ( $\geq 98\%$  *Z*) in 82% yield (55% from propyne). Compound **9** promises to serve as a useful intermediate for the synthesis of (+)-calyculin A<sup>20</sup> and related compounds (Equation 3 of Scheme 1).

In summary, the following new findings have been obtained: Firstly, contrary to all previous reports, bromoboration of propyne with BBr<sub>3</sub> proceeds in  $\geq 98\%$  *syn*-selectivity to produce (*Z*)-2-bromo-1-propenyldibromoborane (**1**) in excellent yield. Secondly, although **1** is readily prone to stereoisomerization, it can be converted to (*Z*)-2-bromo-1-propenyl(pinacoly)borane (**2**) of  $\geq 98\%$  isomeric purity in 85% yield from propyne. Thirdly, Pd-catalyzed cross-coupling of **2** with a wide variety of organozincs containing *n*-, *i*-, *c*-alkyl, allyl, benzyl, homoallyl, homobenzyl, homopropargyl, alkenyl, aryl, and alkynyl in the presence of Pd catalyst (1 mol % or less) provides the corresponding (*Z*)-alkenylpinacolboronates (**3**) in 73-90% yields as  $\geq 98\%$  isomeric pure compounds. Fourthly, treatment of **3** with I<sub>2</sub> (2 equiv) and NaOH (3 equiv) in THF-H<sub>2</sub>O at 23 °C for 1 h affords the corresponding alkenyliodides (**4**) in 80-90% yields as  $\geq 98\%$  isomerically pure compounds. Fifthly, the propyne bromoboration-based (*Z*)-trisubstituted alkene syntheses herein reported promises to provide an unprecedentedly stereoselective ( $\geq 98\%$ ) and widely applicable route to methyl-branched (*Z*)-trisubstituted alkenes of biological and medicinal significance, as indicated by highly efficient and selective syntheses of (3*Z*, 6*E*)- $\alpha$ -farnesene<sup>16</sup> (**6**) as well as proven and promising intermediates for the syntheses of mycolactone A<sup>17,18</sup> and (+)-calyculin A.<sup>20</sup>

## Supplementary Material

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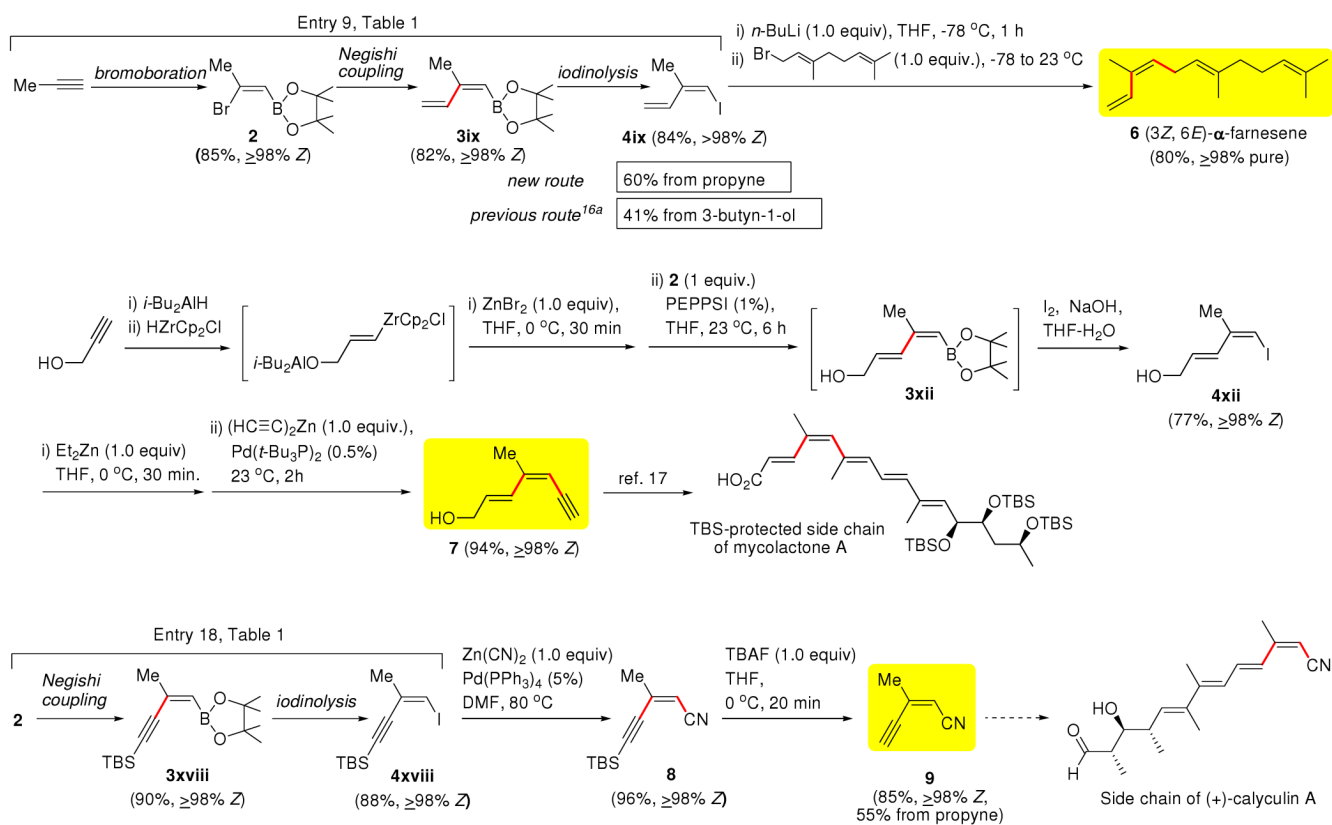
## Acknowledgments

We thank the National Institutes of Health (GM 36792) and Purdue University for support of this research. We also thank Sigma-Aldrich, Albemarle, and Boulder Scientific for their support.

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**Scheme 1.**

Some (Z)-1-Iodo-2-methyl-1-alkenes of Interest in Efficient and Selective Syntheses of (Z)-Trisubstituted Alkene-Containing Natural Products.

Table 1

Highly ( $\geq 98\%$ ) Selective Conversion of 1-Propyne to (Z)-2-Bromo-1-alkenylboronates (**2**) by Bromoboration and Their Negishi Coupling-Iodinolysis to Produce **3** and **4** of  $\geq 98\%$  Isomeric Purity.

entry	R	suffix to 3 and 4		3 <sup>a</sup>		4 <sup>a</sup>	
		isolated yield (%)	NOE (%)	isolated yield (%)	NOE (%)	isolated yield (%)	NOE (%)
1	<i>n</i> -Hex	i	87	2.8	86	1.4	
2	<i>i</i> -Bu	ii	86	2.9	82	2.8	
3	<i>c</i> -Hex	iii	84	4.6	88	2.0	
4	Me <sub>2</sub> C=CHCH <sub>2</sub>	iv	79	2.7	84	1.9	
5	PhCH <sub>2</sub>	v	83	2.9	81	1.3	
6	Me <sub>2</sub> C=CCH <sub>2</sub> CH <sub>2</sub>	vi	73	3.1	87	2.4	
7	PhCH <sub>2</sub> CH <sub>2</sub>	vii	76	4.8	80	1.3	
8	<i>n</i> -HexC≡CCH <sub>2</sub> CH <sub>2</sub>	viii	79	4.6	90	3.5	
9	CH <sub>2</sub> =CH	ix	82	5.0	84	1.4	
10	( <i>E</i> )- <i>n</i> -HexCH=CH	x	96	4.1	- <sup>b</sup>	-	
11	( <i>E</i> )- <i>n</i> -HexC(Me)=CH	xi	83	3.2	81	1.2	
12	( <i>E</i> )-HOCH <sub>2</sub> CH=CH	xii	- <sup>c</sup>	-	77 <sup>d</sup>	2.1	
13	( <i>E</i> )-TBSOCH <sub>2</sub> C=CH	xiii	90	3.7	84	1.5	
14	Ph	xiv	86	3.5	86	1.3	
15	4-MeOC <sub>6</sub> H <sub>4</sub>	xv	87	3.7	89	1.3	
16	4-ClC <sub>6</sub> H <sub>4</sub>	xvi	85	3.7	85	1.4	
17	<i>n</i> -BuC≡C	xvii	83	1.9	87	1.3	
18	TBSC≡C	xviii	90 <sup>e</sup>	6.1	88	1.2	

<sup>a</sup>The isomeric purity of **3** and **4** are uniformly  $\geq 98\%$ . The overall isomeric purity was determined by <sup>13</sup>C NMR spectroscopy, and the alkene geometry was determined by <sup>1</sup>H NMR NOE measurements.

<sup>b</sup>Iodolysis was not performed in this case.

<sup>c</sup>For further details, see Scheme 1. In this case, PEPPSI (1%) was used instead of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (1%). Compound **3xii** was crudely obtained and directly used for its conversion to **4xii**.

<sup>d</sup>Overall yield from propyne and propargyl alcohol.

<sup>e</sup>In this case, Pd(*r*-Bu<sub>3</sub>P)<sub>2</sub> (0.1%) was used instead of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (1%).