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

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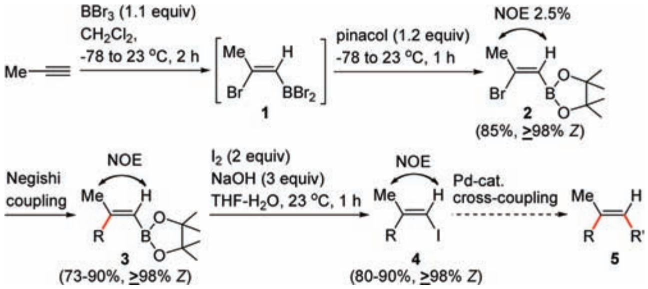
ABSTRACT



Contrary to all previous reports, bromoboration of propyne with BBr_3 proceeds in ≥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 ≥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 ≥98% *Z*.

Zr-catalyzed carboalumination of alkynes,[1] especially methylalumination (ZMA, hereafter), has been widely used for the synthesis of (*E*)-trisubstituted alkenes, especially those of the terpenoid origin.[2] Although the corresponding methylcupration of alkynes has not been well developed, alkylcupration[3] 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 those cases where alkylmetals including allyl- and benzylmetals are used. Haloboration reported in 1964 by Lappert[4] 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[5] and more recently by Wang[6] with a double Negishi coupling process, these previous studies collectively fell short of the above-stated promise. Notably, in the single most desirable

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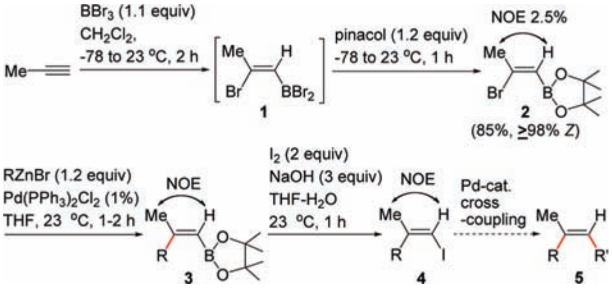
Table 1. Highly (−98%) Selective Conversion of 1-Propyne to (*Z*)-2-Bromo-1-alkenylboronates (**2**) by Bromoboration and Their Negishi Coupling−Iodinolysis to Produce **3** and **4** of ≥98% Isomeric Purity



entry	R	suffix to **3** and **4**	**3**[a] isolated yield (%)	**3**[a] NOE (%)	**4**[a] isolated yield (%)	**4**[a] NOE (%)
1	*n*-Hex	i	87	2.8	86	1.4
2	*i*-Bu	ii	86	2.9	82	2.8
3	*c*-Hex	iii	84	4.6	88	2.0
4	$Me_2C{=}CHCH_2$	iv	79	2.7	84	1.9
5	$PhCH_2$	v	83	2.9	81	1.3
6	$Me_2C{=}CCH_2CH_2$	vi	73	3.1	87	2.4
7	$PhCH_2CH_2$	vii	76	4.8	80	1.3
8	*n*-HexC≡CCH_2CH_2	viii	79	4.6	90	3.5
9	$CH_2{=}CH$	ix	82	5.0	84	1.4
10	(*E*)-*n*-HexCH═CH	x	96	4.1	-[b]	-
11	(*E*)-*n*-HexC(Me)═CH	xi	83	3.2	81	1.2
12	(*E*)-$HOCH_2CH{=}CH$	xii	-[c]	-	77[d]	2.1
13	(*E*)-$TBSOCH_2C{=}CH$	xiii	90	3.7	84	1.5
14	Ph	xiv	86	3.5	86	1.3
15	4-$MeOC_6H_4$	xv	87	3.7	89	1.3
16	4-ClC_6H_4	xvi	85	3.7	85	1.4
17	*n*-BuC≡C	xvii	83	1.9	87	1.3
18	TBSC≡C	xviii	90[e]	6.1	88	1.2

[a] The isomeric purities of **3** and **4** are uniformly ≥98%. The overall isomeric purity was determined by ^{13}C NMR spectroscopy, and the alkene geometry was determined by ^{1}H NMR NOE measurements. [b] Iodinolysis was not performed in this case. [c] For further details, see Scheme 1. In this case, PEPPSI (1%) was used instead of $Pd(PPh_3)_2Cl_2$ (1%). Compound **3xii** was crudely obtained and directly used for its conversion to **4xii**. [d] Overall yield from propyne and propargyl alcohol. [e] In this case, Pd(*t*-$Bu_3P)_2$ (0.1%) was used instead of $Pd(PPh_3)_2Cl_2$ (1%).

case of propyne haloboration for the selective synthesis of (*Z*)-alkene-containing terpenoids, all reported stereoselectivity values were ≤89%.[6c,8,9] Second, 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,[8a,9a,10] those subjected to Pd-catalyzed cross-coupling have been strictly limited to the cases of alkyl-substituted alkynes.[5−7]

We herein report that, contrary to the previous claim,[8b] *bromoboration of propyne with* BBr_3 *does proceed in ≥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 condtions, *it can be converted to the corresponding cyclic boronate (***2***) of ≥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)[11] including alkyl, allyl, benzyl, alkenyl, aryl, and alkynyl groups proceeds to give **3** in high yields with full retention (≥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.[1−3] Our brief survey of the metal countercations (M) of the organometallic reagents (RM) for the substitution of Br with a carbon group (R) has indicated Zn is indeed the most satisfactory metal countercation, 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 ≤2% (M = Mg or Al), 82% (M = In), 18% (M = Cu), and 73% (M = Zr).

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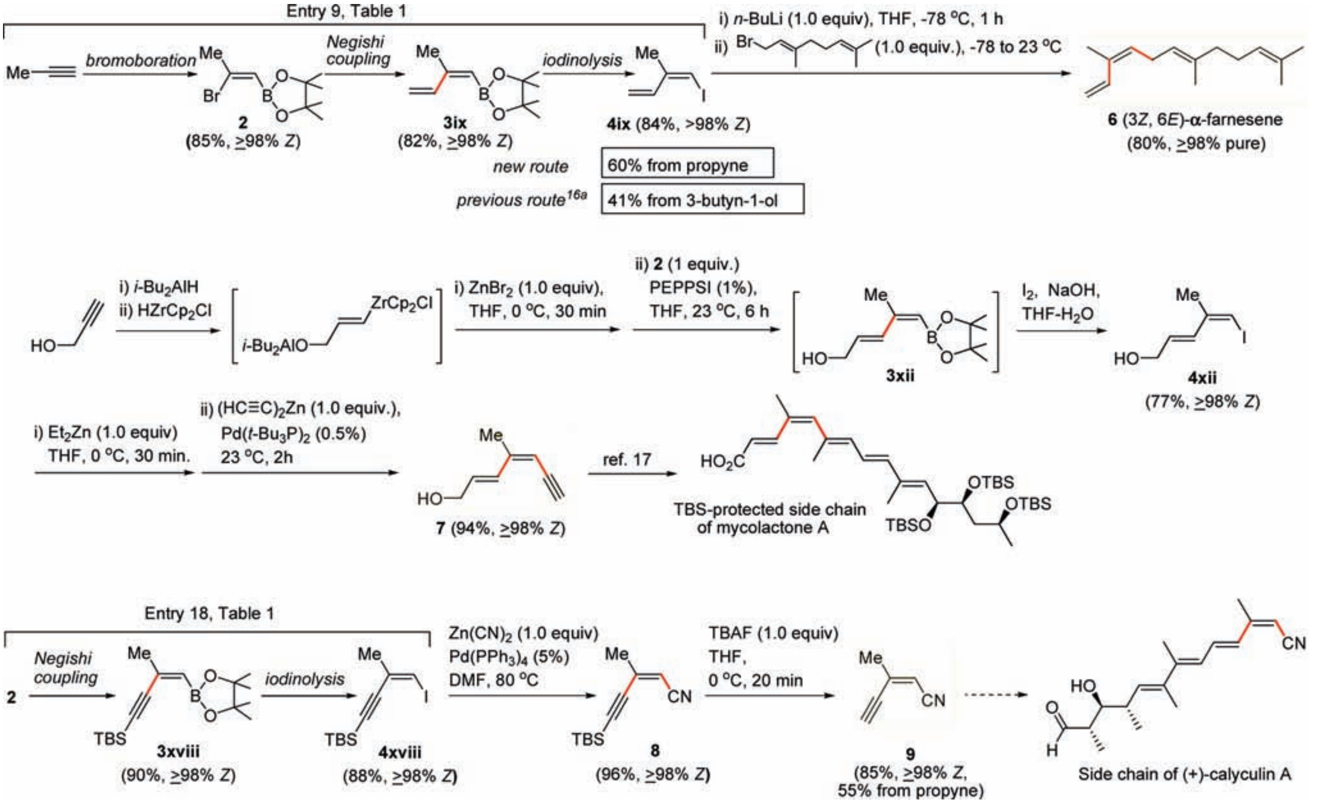
Scheme 1. Some (*Z*)-1-Iodo-2-methyl-1-alkenes of Interest in Efficient and Selective Syntheses of (*Z*)-Trisubstituted Alkene-Containing Natural Products



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[12] of **3**. However, direct Pd-catalyzed Suzuki coupling of (*Z*)-*β*-substituted alkenylboranes with alkenyl and alkynyl halides run under the previously reported conditions[5] has tended to give the desired products in relatively low (<50−60%) yields.[5,13] 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.[11] As shown in Table 1, alkenyl iodides (**4**) required in the latter protocol are obtained by treatment of **3** with I_2 (2 equiv) and NaOH (3 equiv) in THF and H_2O at 23 °C[14] in uniformly high yields of 80−90% with full (≥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 (≥98%) selective route to (*Z*)-2-methyl-1-alkenylboranes (**3**) and the corresponding iodides (**4**)[15] 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 (≥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 ≥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[16] (eq 1 of Scheme 1). It should be remembered that treatment of **4ix** with just 1 equiv of *n*-BuLi followed by addition of geranyl bromide of ≥98% isomeric purity furnished (3*Z*,6*E*)-α-farnesene (**6**) of ≥98% isomeric purity in 80% yield without using any catalyst.[16] We recently reported the preparation of a key intermediate **7** for the synthesis of the side chain of

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(13) For difficulties associated with some *β*-(*Z*)-alkenylboranes in Pd-catalyzed alkenyl−alkenyl coupling, see also: Huang, Z.; Negishi, E. *J. Am. Chem. Soc.* **2007**, *129*, 14788–14792.

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mycolactone A[17,18] from propargyl alcohol in 42% yield over six steps and ≥98% selectivity.[17] The same compound **7** can now be synthesized from propyne and propargyl alcohol in a mere two steps in 62% overall yield (eq 2 of Scheme 1). Finally, treatment of **2** with TBSC≡CZnBr in the presence of 0.1 mol % of Pd(t-Bu$_3$P)$_2$ and with I$_2$ and NaOH gave iodoenyne **4xviii** (≥98% *Z*) in 79% yield. Pd-catalyzed cyanation[19] of **4xviii** with Zn(CN)$_2$ in the presence of Pd(PPh$_3$)$_4$ followed by desilylation with TBAF provided **9** (≥98% *Z*) in 82% yield (55% from propyne). Compound **9** promises to serve as a useful intermediate for the synthesis of (+)-calyculin A[20] and related compounds (eq 3 of Scheme 1).

In summary, the following new findings have been obtained: First, contrary to all previous reports, bromoboration of propyne with BBr$_3$ prodeeds in ≥98% *syn*-selectivity to produce (*Z*)-2-bromo-1-propenyldibromoborane (**1**) in excellent yield. Second, although **1** is readily prone to stereoisomerization, it can be converted to (*Z*)-2-bromo-1-propenyl(pinacolyl)borane (**2**) of ≥98% isomeric purity in 85% yield from propyne. Third, 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 ≥98% isomeric pure compounds. Fourth, treatment of **3** with I$_2$ (2 equiv) and NaOH (3 equiv) in THF−H$_2$O at 23 °C for 1 h affords the corresponding alkenyliodides (**4**) in 80−90% yields as ≥98% isomerically pure compounds. Fifth, the propyne bromoboration-based (*Z*)-trisubstituted alkene syntheses herein reported promises to provide an unprecedentedly stereoselective (≥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*)-α-farnesene[16] (**6**) as well as proven and promising intermediates for the syntheses of mycolactone A[17,18] and (+)-calyculin A.[20]

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

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