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Arylethyne Bromoboration–Negishi Coupling Route to *E*- or *Z*-Aryl-Substituted Trisubstituted Alkenes of ≥98% Isomeric Purity. New Horizon in the Highly Selective Synthesis of Trisubstituted Alkenes

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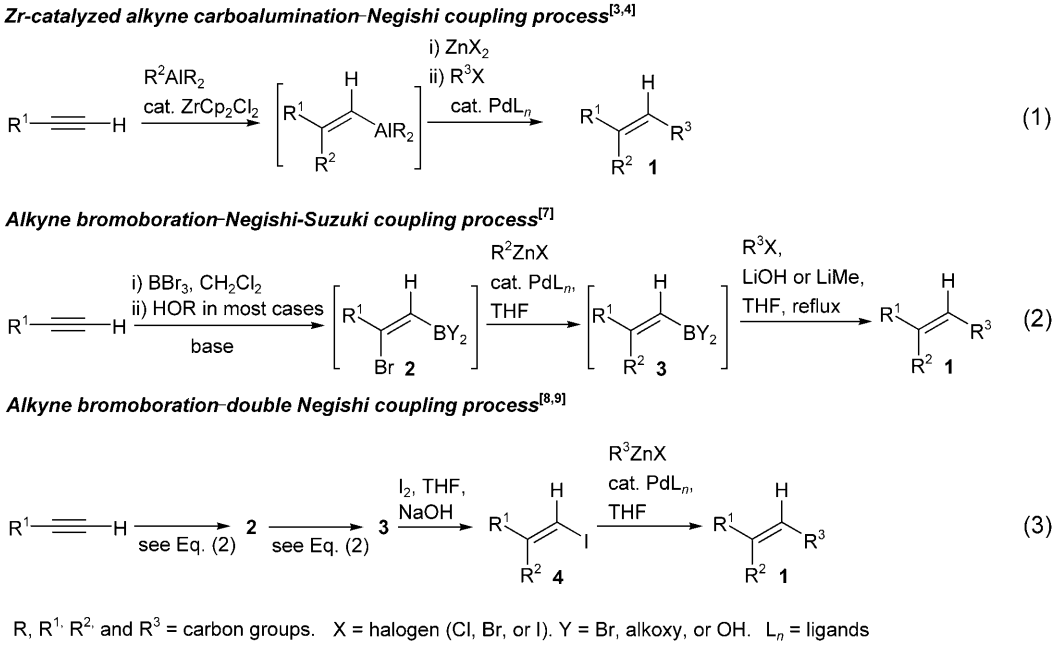
Abstract: The hitherto unprecedented palladium-catalyzed cross-coupling of (*Z*)-β-bromo-β-arylethenylboranes can be made to proceed satisfactorily through (1) the use of highly catalytically active bis(tri-*tert*-butylphosphine)palladium or dichloro[*N*,*N*-bis-(2,6-diisopropylphenyl)imidazol-2-yl](*m*-chloropyridine)palladium and (2) conversion of the dibromoboryl group to the (pinacol)boryl group. Thus, a wide variety of carbon groups can be used to substitute bromine in ≥98% stereo- and regioselectivity, while suppressing the otherwise dominant β-debromoboration. Together with the alkylethyne-based protocols, the alkyne bromoboration–Negishi coupling tandem process has emerged as the most widely applicable and highly selective route to trisubstituted alkenes including those that are otherwise difficult to access.

Keywords: arylethyne bromoboration; bis(tri-*tert*-butylphosphine)palladium; (*Z*)-β-bromo-β-arylethenylboranes; dichloro[*N*,*N*-bis-(2,6-diisopropylphenyl)imidazol-2-yl](*m*-chloropyridine)palladium; Negishi coupling

Despite major advances in the syntheses of strictly (≥98%) regio- and stereodefined alkenes *via* "elementometalation"[1] Pd- or Ni-catalyzed cross-coupling developed since 1976,[2–4] efficient and highly (≥98%) selective syntheses of tri- and tetrasubstituted alkenes continue to provide major synthetic challenges. The Zr-catalyzed alkyne carboalumination-Negishi coupling[3,4] [Eq. (1) in Scheme 1] has provided a highly selective and widely used method for the synthesis of trisubstituted alkenes.[4b] Although this method is broad in synthetic scope with respect to R^1 of the starting alkyne ($R^1C{\equiv}CH$), the R^2 group of the organoalanes to be added to $R^1C{\equiv}CH$ has been practically limited to Me and a limited number of alkyl groups including allyl and benzyl groups.[3–6] On the other hand, in an alkyne bromoboration–Negishi–Suzuki tandem cross-coupling process [Eq. (2) in Scheme 1] reported by Suzuki in 1988,[7] bromoboration of $R^1C{\equiv}CH$ is followed by incorporation of both R^2 and R^3 groups by Pd-catalyzed cross-coupling reactions of wide synthetic scopes, thereby promising to provide a method of very wide applicability for synthesizing trisubstituted alkenes. In reality, however, all reported examples[7] of Eq. (2) in Scheme 1 and of its modification involving double Negishi coupling reactions[8,9] [Eq. (3) in Scheme 1] involve the use of only alkylethynes, even though haloborations of aryl- and alkenyl-substituted ethynes are known to proceed well.[10]

As readily suspected, competitive debromoboration of **2** to revert to the starting alkynes would be the main cause of difficulty in the Pd-catalyzed cross-coupling of **2**, and the fact that those derived from aryl- and alkenyl-substituted ethynes are benzylic and allylic bromides, respectively, besides being alkenyl bromides must undoubtedly be responsible for their significantly higher propensity to undergoing debromoboration, as compared with that of alkylethyne-derived **2**. Thus, for example, the reaction of **2a**, generated by bromoboration of phenylethyne followed by treatment with pinacol, with (*E*)-1-octenylzinc bromide in the presence of $Pd(DPEphos)Cl_2$ (0.5 mol%) at 23 °C for 2 h led to the formation of the desired **3a**



Scheme 1. Highly (≥98%) selective "elementometalation"–Pd-catalyzed cross-coupling routes to trisubstituted alkenes.

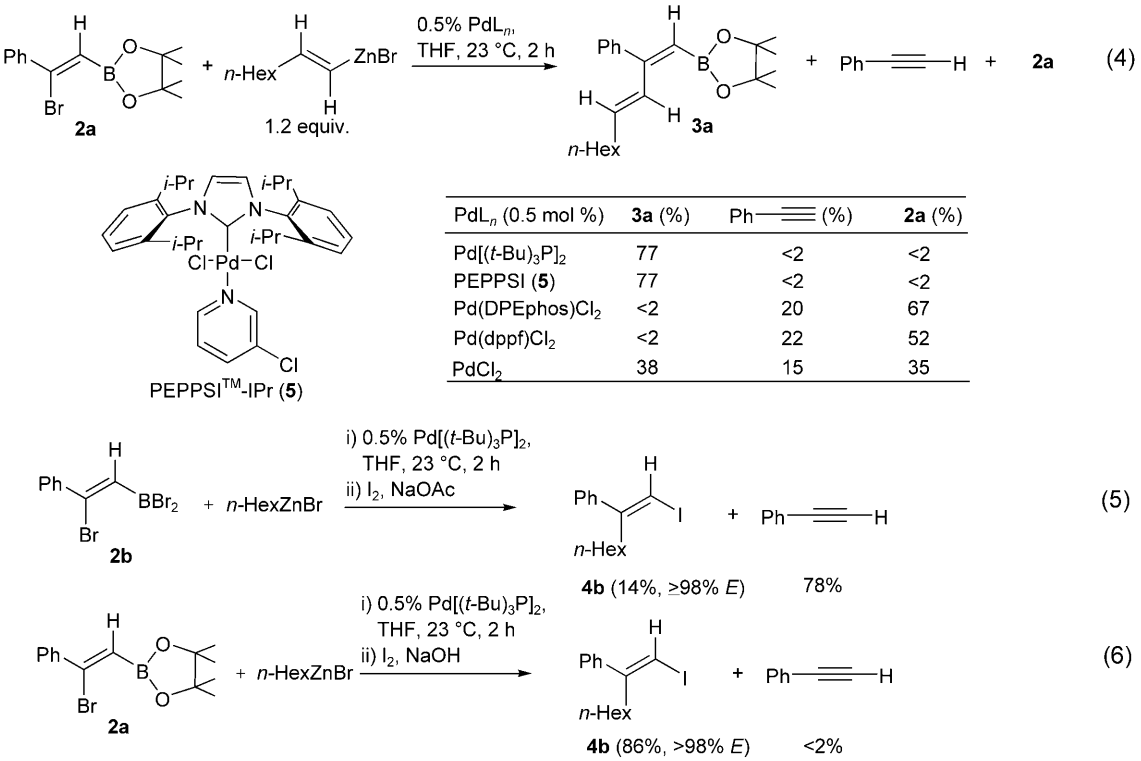
in <2% yield along with PhC≡CH (20%) and the unreacted **2a** (67%). The results indicate that the reaction not only is slow but also produces at least ten times as much PhC≡CH as **3a**.

To our delight, however, the use of highly active Pd catalysts, such as Pd[(*t*-Bu)$_3$P]$_2$[11,12] and PEPPSI™-IPr (**5**),[12c,13,14] almost fully suppressed debromoboration of **2a** and led to the production of the desired **3a** of ≥98% isomeric purity in high yields along with only traces (<2%) of PhC≡CH and the unreacted starting compound **2a** [Eq. (4) in Scheme 2]. Earlier in this study, we treated **2b** (Y=Br) with *n*-HexZnBr in THF in the presence of 0.5 mol% of Pd[(*t*-Bu]$_3$P]$_2$ and obtained, after iodinolysis, the desired (*E*)-α-(*n*-hexyl)-β-iodostyrene (**4b**) only in 14% yield along with PhC≡CH formed in 78% yield [Eq. (5) in Scheme 2]. However, the use of Pd[(*t*-Bu)$_3$P]$_2$ as a catalyst later proved to be appropriate, since its use along with **2a** in place of **2b** gave **4b** in 86% yield [Eq. (6) in Scheme 2]. The results shown in Scheme 2 clearly indicate that proper selection of not only Pd catalysts, e.g., Pd[(*t*-Bu)$_3$P]$_2$ and PEPPSI™-IPr (**5**), but also boryl groups, e.g., pinacolboryl rather than dibromoboryl, is critically important.

As summarized in Table 1, a wide range of R^2 groups including alkyl, alkenyl, aryl, and alkynyl may now be introduced into **3** and **4** derived from arylethynes, such as phenylethyne, *p*-chlorophenylethyne, and *p*-tolylethyne, by using (i) (*Z*)-β-aryl-β-bromoalkenyl(pinacol)boranes (**2**), (ii) either Pd[(*t*-Bu)$_3$P]$_2$ or PEPPSI™-IPr (**5**). Since a wide range of Pd-catalyzed alkenylation reactions are known to selectively and satisfactorily convert alkenylmetals and/or alkenyl halides represented by **3** and **4** into the corresponding trisubstituted alkenes **1**[4,15] our attention in this study is focused on the synthesis of **3** and **4**. Many of the alkenes represented by **3** and **4** shown in Table 1 are very difficult to prepare in a highly (≥98%) selective manner by any previously known methods except for those that are accessible by Zr-catalyzed carboalumination[5] and carbocupration[16] of alkynes. To demonstrate the synthetic utility of the alkyne bromoboration–Pd-catalyzed cross-coupling route to **3** and **4**, a pair of (*E*)- and (*Z*)-2-iodo-1,1-diarylethenes **4h** and **4i** were synthesized as ≥98% stereoisomerically pure compounds in 42% and 46% yields in two steps from PhC≡CH and *p*-ClC$_6$H$_4$C≡CH, respectively (Scheme 3).

In summary, the following findings have significantly contributed to the development of the widely applicable and highly selective route to trisubstituted alkenes *via* alkyne elementometalation–Pd-catalyzed cross-coupling.

Firstly, (*Z*)-β-bromo-β-arylethenyldibromoboranes, readily preparable by treatment of arylethyne with BBr$_3$,[10] do not satisfactorily undergo Pd-catalyzed cross-coupling due to competitive β-debromoboration under all conditions tested thus far. However, the combined use of the corresponding (*Z*)-β-bromo-β-arylethenyl(pinacol)boranes and highly active Pd catalysts, such as Pd[(*t*-Bu)$_3$P]$_2$[11,12] and PEPPSI™-IPr (**5**),[13] leads to highly (≥98%) regio- and stereoselective syntheses of the corresponding trisubstituted alkenyl(pinacol)boranes (**3**) in one or two steps from arylethynes *via* Negishi coupling in 53 to 66% isolated overall yields. The corresponding alkenyl iodides (**4**)



PdL$_n$ (0.5 mol %)	**3a** (%)	Ph—≡ (%)	**2a** (%)
Pd[(*t*-Bu)$_3$P]$_2$	77	<2	<2
PEPPSI (**5**)	77	<2	<2
Pd(DPEphos)Cl$_2$	<2	20	67
Pd(dppf)Cl$_2$	<2	22	52
PdCl$_2$	38	15	35

Scheme 2. Pd-catalyzed cross-coupling reactions of (*Z*)-β-bromo-β-phenylethenylboranes (**2a** and **2b**). Effects of Pd catalysts and boryl groups.

can be obtained as ≥98% isomerically pure compounds by known iodinolysis of **3** with I_2 and NaOH in 80–86% isolated yields from **3**. In a couple of cases, the feasibility of one-pot conversion of arylethynes to **4** in *ca.* 60% overall yields has also been demonstrated (Table 1).

Secondly, the arylethyne bromoboration–Negishi coupling protocol reported herein makes available **3** and **4**, and hence their fully carbo-trisubstituted derivatives as well,[4,15] many of which have been very difficult to prepare as highly (≥98%) isomerically pure compounds by any other known methods. Together with the related alkylethyne-based protocols,[7–9] the alkyne bromoboration–Negishi coupling protocol represents the hitherto most widely applicable and highly (≥98%) selective route to trisubstituted alkenes.

Further development with the use of conjugated 1,3-enynes and 1,3-diynes is currently in progress.

Experimental Section

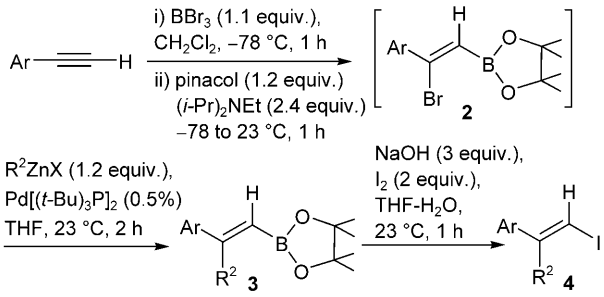
(*Z*)-β-Bromo-β-phenylethenyl(pinacol)borane (2a)

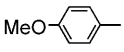
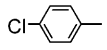
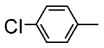
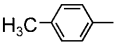
To a stirred solution of BBr_3 (2.08 mL, 22 mmol) in dry CH_2Cl_2 (10 mL) was added phenylethyne (2.20 mL, 20 mmol) at −78 °C. After stirring for 1 h at −78 °C, a solution of pinacol (2.84 g, 24 mmol) and (*i*-Pr)$_2$NEt (8.36 mL, 48 mmol) in dry CH_2Cl_2 (20 mL) was added. The resultant reaction mixture was warmed to 23 °C, stirred for 1 h, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, 98:2 hexane-EtOAc) to give **2a**; yield: 4.51 g (73%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.36$ (s, 12H), 6.44 (s, 1H), 7.3–7.4 (m, 3H), 7.55–7.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 27.74$ (4C), 83.29 (2C), 119–122 (br s), 127.47 (2C), 128.08 (2C), 129.21, 140.06, 140.86; HR-MS: $m/z = 308.0588$, calcd. for $C_{14}H_{18}BBrO_2$ $[M]^+$: 308.0583.

(1*E*,3*E*)-2-Phenyl-1,3-decadienyl(pinacol)borane (3a): Representative Procedure for the Synthesis of β,β-Disubstituted Alkenyl(pinacol)boranes (3)

To a stirred solution of BBr_3 (0.11 mL, 1.1 mmol) in dry CH_2Cl_2 (2 mL) was added phenylethyne (102 mg, 0.11 mL, 1 mmol) at −78 °C. After stirring at −78 °C for 1 h, a solution of pinacol (142 mg, 1.2 mmol) and (*i*-Pr)$_2$NEt (310 mg, 0.42 mL, 2.4 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was warmed to 23 °C and stirred for 1 h. In another flask, Pd[(*t*-Bu)$_3$P]$_2$ (2.6 mg, 0.005 mmol) was dissolved in dry THF (2 mL) and treated consecutively with (*E*)-1-octenylzinc bromide [1.2 mmol, generated by treating (*E*)-1-iodo-1-octene (0.30 g, 1.2 mmol) with *n*-BuLi (0.53 mL, 1.3 mmol, 2.5 M solution in hexanes) in dry THF (2 mL) for 30 min at −78 °C, followed by treatment with a solution of $ZnBr_2$ (0.27 g, 1.2 mmol) in dry THF (2 mL) for 30 min at 0 °C] and (*Z*)-β-phenyl-β-bromoethenyl-(pinacol)borane **2a** generated as described above at 23 °C.

Table 1. Arylethyne bromoboration–Negishi coupling route to β,β-disubstituted alkenyl(pinacol)boranes (**3**) and the corresponding iodides (**4**).



Ar	R^2	Product Yield [%] $3^{[a,b]}$	$4^{[a,c]}$
Ph	*n*-Hex	66	86
Ph	*i*-Bu	64	85
Ph		60	85
Ph	H_2C=CH-	59	83
Ph	(*E*)-*n*-HexCH=CH-	60	85
Ph	(*E*)-*n*-HexCH_3C=CH-	59	85
Ph	*n*-HexC≡C-	–[d]	57[e]
Ph		53	81
Ph		53	80
	Ph	57	81
	*n*-Bu	–[d]	63[f]

[a] Isolated yields of ≥98% pure compounds. The indicated stereochemical assignments were made by NOE measurements.
[b] Yields are based on arylethyne.
[c] Yields are based on **3**.
[d] Compound **3** was crudely obtained and directly used for its conversion to **4**.
[e] Overall yield from phenylethyne.
[f] Overall yield from *p*-tolylethyne.

After stirring for 2 h at 23 °C, the reaction mixture was quenched with 0.5 M HCl, extracted with Et_2O, washed with brine, dried, filtered, concentrated, and purified by column chromatography (silica gel, 98:2 hexane-EtOAc) to give (1*E*,3*E*)-2-phenyl-1,3-decadienyl(pinacol)borane **3a** as a pale yellow oil; yield: 204 mg (60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, J = 6.6 Hz, 3H), 1.50 (s, 12H), 1.2–1.7 (m, 8H), 2.33 (m, 2H), 5.52 (s, 1H), 5.8–5.9 (m, 1H), 7.37 (d, J = 15.7 Hz, 1H), 7.3–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.27, 22.77, 25.65 (4C), 29.02, 29.09, 31.92, 33.27, 83.19 (2C), 117–120 (br s), 126.53, 127.46, 127.97 (2C), 128.59 (2C), 138.73, 143.50, 160.68; HR-MS: m/z = 340.2571, calcd. for $C_{22}H_{33}BO_2$ $[M]^+$: 340.2574.

Representative Procedure for the Synthesis of β,β-Disubstituted Alkenyl Iodides (4) by Iodinolysis of Pinacolboranes (3)

To a stirred solution of **3i** (170 mg, 0.5 mmol) in THF (1 mL) was added a solution of NaOH (0.5 mL, 1.5 mmol, 3 M in water). The resultant mixture was stirred for 10 min at 23 °C, followed by dropwise addition of a solution of I_2 (0.25 g, 1 mmol) in THF (5 mL). After 1 h at 23 °C, the reaction mixture was quenched with aqueous $Na_2S_2O_3$, extracted with ether, washed successively with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, hexane) to give (*E*)-β-iodo-α-(*p*-chlorophenyl)styrene (**4i**) as a colorless oil; yield: 138 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (s, 1H), 7.18 (d, J = 8.7 Hz, 2H), 7.25–7.3 (m, 3H), 7.28 (d, J = 8.7 Hz, 2H), 7.4–7.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.53, 128.14, 128.40 (2C), 128.48 (2C), 128.73 (2C), 129.30 (2C), 133,98, 139.47, 141.28, 151.44; HR-MS: m/z = 339.9512, calcd. for $C_{10}H_{14}ClI$ $[M]^+$: 339.9516.

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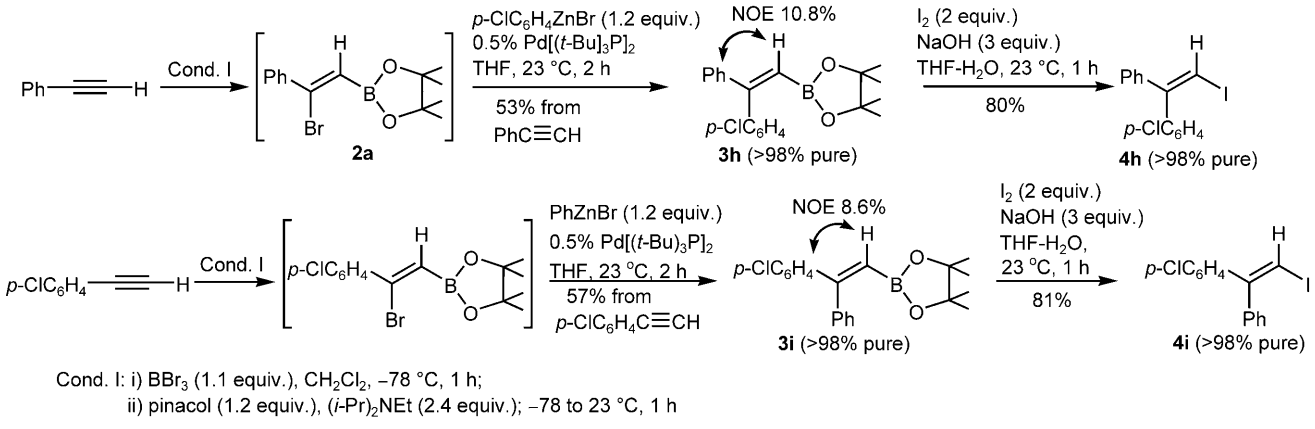

Scheme 3. Highly selective (≥98%) synthesis of (*E*)- and (*Z*)-α-(*p*-chlorophenyl)-β-iodostyrenes (**4h** and **4i**) *via* arylethyne bromoboration–Negishi coupling–iodinolysis.

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