Published in final edited form as:

Adv Synth Catal. 2010 March 8; 352(4): 627–631. doi:10.1002/adsc.200900766.

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

Chao Wang^a, Zhaoqing Xu^a, Tomas Tobrman^{a,b}, and Ei-ichi Negishi^a

Ei-ichi Negishi: negishi@purdue.edu

^aHerbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Dr., West Lafayette, IN 47907-2084, USA. Fax: (+1)-765-494-0239

^bDepartment of Organic Chemistry, Prague Institute of Chemical Technology, Technicka 5, 166 28 Prague 6, Czech Republic

Abstract

The hitherto unprecedented palladium-catalyzed cross-coupling of (*Z*)-*arylethenyl*boranes 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 dibromoboryl group to (pinacol)boryl group. Thus, a wide variety of carbon groups can be used to substitute bromine in $\geq 98\%$ stereo- and regioselectivity, while suppressing the otherwise dominant *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; Negishi coupling; (*Z*)-*arylethenyl*boranes; bis(tri-*tert*-butylphosphine)palladium; dichloro[*N,N*-bis-(2,6-diisopropylphenyl)imidazol-2-yl](*m*-chloropyridine)palladium

Despite major advances in the syntheses of strictly ($\geq 98\%$) regio- and stereodefined alkenes via “elementometalation”^[1]–Pd- or Ni-catalyzed cross-coupling developed since 1976,^{[2]–[4]} efficient and highly ($\geq 98\%$) 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 R¹ of the starting alkyne (R¹C–CH), the R² group of the organoalanes to be added to R¹C–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 R¹C–CH is followed by incorporation of both R² and R³ groups by Pd-catalyzed cross-coupling reactions of wide synthetic scopes, thereby

Correspondence to: Ei-ichi Negishi, negishi@purdue.edu.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200900766>.

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 haloboration 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)Cl₂ (0.5 mol %) at 23 °C for 2 h led to the formation of the desired **3a** 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(^tBu₃P)₂^[11,12] and PEPPSITM-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. 1 in Scheme 2). Earlier in this study, we treated **2b** (Y = Br) with ⁷HexZnBr in THF in the presence of 0.5 mol % of Pd(^tBu₃P)₂ and obtained, after iodinolysis, the desired (*E*)-*n*-hexyl-iodostyrene (**4b**) only in 14% yield along with PhC=CH formed in 78% yield (Eq. 2 in Scheme 2). However, the use of Pd(^tBu₃P)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. 3 in Scheme 2). The results shown in Scheme 2 clearly indicate that proper selection of not only Pd catalysts, e.g., Pd(^tBu₃P)₂ and PEPPSITM-IPr (**5**), but also boryl groups, e.g., pinacolboryl rather than dibromoboryl, is critically important.

As summarized in Table 1, a wide range of R² groups including alkyl, alkenyl, aryl, and alkynyl may now be introduced into **3** and **4** derived from aryethynes, such as phenylethyne, *p*-chlorophenylethyne, and *p*-tolylethyne, by using (i) (*Z*)-*n*-aryl-*n*-bromoalkenyl(pinacol)boranes (**2**), (ii) either Pd(^tBu₃P)₂ or PEPPSITM-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*-ClC₆H₄C=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.

(1) (*Z*)-*n*-Bromo-*n*-arylethyndibromoboranes, readily preparable by treatment of aryethyne with BBr₃,^[10] do not satisfactorily undergo Pd-catalyzed cross-coupling due to competitive *n*-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*Bu₃P)₂ [11,12] and PEPPSITM-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 arylethyne via Negishi coupling in 53 to 66% isolated overall yields. The corresponding alkenyl iodides (**4**) can be obtained as >98% isomerically pure compounds by known iodinolysis of **3** with I₂ and NaOH in 80–86% isolated yields from **3**. In a couple of cases, the feasibility of one-pot conversion of arylethyne to **4** in ca. 60% overall yields has also been demonstrated (Table 1).

(2) The arylethyne bromoboration–Negishi coupling protocol reported herein makes available **3** and **4**, and hence their fully carboborotrisubstituted 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 BBr₃ (2.08 mL, 22 mmol) in dry CH₂Cl₂ (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 *t*Pr₂NEt (8.36 mL, 48 mmol) in dry CH₂Cl₂ (20 mL) was added. The resultant reaction mixture was warmed to 23 °C, stirred for 1 h, washed with brine, dried over Na₂SO₄, filtered, concentrated, and purified by column chromatography (silica gel, 98:2 hexane-EtOAc) to give 4.51 g (73%) of **2a**. ¹H NMR (300 MHz, CDCl₃) 1.36 (s, 12 H), 6.44 (s, 1 H), 7.3–7.4 (m, 3 H), 7.55–7.65 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) 27.74 (4 C), 83.29 (2 C), 119–122 (br s), 127.47 (2 C), 128.08 (2 C), 129.21, 140.06, 140.86. HRMS calcd for C₁₄H₁₈BBroO₂ [M]⁺: 308.0583. Found 308.0588.

(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 BBr₃ (0.11 mL, 1.1 mmol) in dry CH₂Cl₂ (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 *t*Pr₂NEt (310 mg, 0.42 mL, 2.4 mmol) in dry CH₂Cl₂ (2 mL) was added. The reaction mixture was warmed to 23 °C and stirred for 1 h. In another flask, Pd(*t*Bu₃P)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 ZnBr₂ (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. After stirring for 2 h at 23 °C, the reaction mixture was quenched with 0.5 M HCl, extracted with Et₂O, washed with brine, dried, filtered, concentrated, and purified by column chromatography (silica gel, 98:2 hexane-EtOAc) to give 204 mg (60%) of (1*E*,3*E*)-2-phenyl-1,3-decadienyl(pinacol)borane **3a** as a pale yellow oil. This one-pot procedure is operationally simpler and somewhat higher yielding than the two step synthesis of **3**. ¹H NMR (300 MHz, CDCl₃) 1.07 (t, *J* = 6.6 Hz, 3 H), 1.50 (s, 12 H), 1.2–1.7 (m, 8 H), 2.33 (m, 2 H), 5.52 (s, 1 H), 5.8–5.9 (m, 1 H), 7.37 (d, *J* = 15.7 Hz, 1H), 7.3–7.4 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) 14.27, 22.77, 25.65 (4 C), 29.02, 29.09, 31.92, 33.27, 83.19 (2 C), 117–120 (br s),

126.53, 127.46, 127.97 (2 C), 128.59 (2 C), 138.73, 143.50, 160.68. HRMS calcd for $C_{22}H_{33}BO_2$ $[M]^+$: 340.2574. Found 340.2571.

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 138 mg (81%) of (*E*)-*i*-iodo- (*p*-chlorophenyl)styrene (**4i**) as a colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 7.18 (d, J = 8.7 Hz, 2 H), 7.25–7.3 (m, 3 H), 7.28 (d, J = 8.7 Hz, 2 H), 7.4–7.5 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.53, 128.14, 128.40 (2 C), 128.48 (2 C), 128.73 (2 C), 129.30 (2 C), 133.98, 139.47, 141.28, 151.44. HRMS calcd for $C_{10}H_{14}ClI$ $[M]^+$: 339.9516. Found 339.9512.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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.

References

1. Hydrometalation, carbometalation, halometalation and other heterometalations as well as various metallometalations may be collectively termed "elementometalation".
2. For seminal works involving hydrometalation, see: Baba S, Negishi E. *J Am Chem Soc.* 1976; 98:6729–6731. Negishi E, Baba S. *J Chem Soc Chem Comm.* 1976:596–597. Negishi E, Van Horn DE. *J Am Chem Soc.* 1977; 99:3168–3170. Okukado N, Van Horn DE, Klima WL, Negishi E. *Tetrahedron Lett.* 1978:1027–1030.
3. For seminal work involving carbometalation, see: Negishi E, Okukado N, King AO, Van Horn DE, Spiegel BI. *J Am Chem Soc.* 1978; 100:2254–2256.
4. For representative early and recent reviews, see: Negishi E. *Acc Chem Res.* 1982; 15:340–348. Negishi E. *Bull Chem Soc Jpn.* 2007; 80:233–257.
5. a) Van Horn DE, Negishi E. *J Am Chem Soc.* 1978; 100:2252–2254. b) Miller JA, Negishi E. *Tetrahedron Lett.* 1984; 25:5863–5866. c) Negishi E, Van Horn DE, Yoshida T. *J Am Chem Soc.* 1985; 107:6639–6647. d) Negishi E, Kondakov DY, Choueiry D, Kasai K, Takahashi T. *J Am Chem Soc.* 1996; 118:9577–9588.
6. For a related alkyne carbocupration–Pd-catalyzed cross-coupling protocol where the carbon groups added via carbocupration are also limited to certain alkyl groups, see: Jabri N, Alexakis A, Normant JF. *Tetrahedron Lett.* 1981; 22:959–962. Jabri N, Alexakis A, Normant JF. *Tetrahedron Lett.* 1982; 23:1589–1592.
7. Satoh Y, Serizawa H, Miyaura N, Hara S, Suzuki A. *Tetrahedron Lett.* 1988; 29:1811–1814. For general reviews of the Pd-catalyzed cross-coupling, see: Miyaura N, Suzuki A. *Chem Rev.* 1995; 95:2457–2483. Kotha S, Lahiri K, Kashinath D. *Tetrahedron.* 2002; 58:9633–9695.
8. a) Wang KK, Wang Z. *Tetrahedron Lett.* 1994; 35:1829–1832. b) Wang KK, Wang Z, Tarli A, Gannett P. *J Am Chem Soc.* 1996; 118:10783–10791. c) Tarli A, Wang KK. *J Org Chem.* 1997; 62:8841–8847.
9. a) Xu Z, Negishi E. *Org Lett.* 2008; 10:4311–4314. [PubMed: 18763786] b) Wang C, Tobrman T, Xu Z, Negishi E. *Org Lett.* 2009; 11:4092–4095. [PubMed: 19694459]

10. a) Lappert MF, Prokai B. *J Organomet Chem.* 1964; 1:384–400. b) Hara S, Dojo H, Takinami S, Suzuki A. *Tetrahedron Lett.* 1983; 24:731–734. c) Hara S, Satoh Y, Ishiguro H, Suzuki A. *Tetrahedron Lett.* 1983; 24:735–738. d) Kabalka GW, Wu Z, Ju Y. *Org Lett.* 2002; 4:1491–1493. [PubMed: 11975611] e) Kabalka GW, Yao ML, Borella S, Wu Z. *Org Lett.* 2005; 7:2865–2867. [PubMed: 15987156] f) Kabalka GW, Yao ML, Borella S, Wu Z. *Chem Commun.* 2005:2492–2494.
11. For seminal work on the use of $t\text{Bu}_3\text{P}$ in the Negishi coupling, see: Dai C, Fu GC. *J Am Chem Soc.* 2001; 123:2719. [PubMed: 11456957]
12. For our earlier use of $t\text{Bu}_3\text{P}$ in related reactions, see: Shi J, Zeng X, Negishi E. *Org Lett.* 2003; 5:1825–1828. [PubMed: 12762662] Shi J, Negishi E. *J Organomet Chem.* 2003; 687:518–524. Zeng X, Qian M, Hu Q, Negishi E. *Angew Chem Int Ed.* 2004; 43:2259–2263.
13. Kantchev EAB, O'Brien CJ, Organ MG. *Angew Chem Int Ed.* 2007; 46:2768–2813.
14. a) Wang G, Huang Z, Negishi E. *Org Lett.* 2008; 10:3223–3226. [PubMed: 18593171] b) Wang G, Huang Z, Negishi E. *Tetrahedron Lett.* 2009; 50:3220–3223.
15. Negishi, E., editor. *Handbook of Organopalladium Chemistry for Organic Synthesis.* Wiley-Interscience; New York: 2002. p. 215–1119. Part III, in particular, Chap. III. 2. 6, pp. 335–408; Chap. III. 2. 14. 2, pp. 721–766; Chap. III. 2. 15, pp. 767–789; Chap. III. 2. 18, pp. 863–942
16. For a review, see: Normant JF, Alexakis A. *Synthesis.* 1981:841–870.

Zr-catalyzed alkyne carboalumination–Negishi coupling process^[3,4] *Alkyne bromoboration–Negishi–Suzuki coupling process*^[7] *Alkyne bromoboration–double Negishi coupling process*^[8,9]

R, R¹, R², and R³ = carbon groups. X = halogen (Cl, Br, or I). Y = Br, alkoxy, or OH. L_n = ligands

Scheme 1.

Highly (98%) selective “elementometalation” –Pd-catalyzed cross-coupling routes to trisubstituted alkenes.

PdL _n (0.5 mol %)	3a (%)	Ph—C≡C—H (%)	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*)-1-bromo-2-phenylethenylboranes (**2a** and **2b**). Effects of Pd catalysts and boryl groups. Cond. I: i) BBr₃ (1.1 equiv), CH₂Cl₂, −78 °C, 1 h; ii) pinacol (1.2 equiv), ^tPr₂NEt (2.4 equiv); −78 to 23 °C, 1 h

Scheme 3.

Highly selective (98%) synthesis of (*E*)- and (*Z*)- -(*p*-chlorophenyl)- -iodostyrenes (**4h** and **4i**) via aryne bromoboration–Negishi coupling–iodinolysis.

Table 1

Arylethyne bromoboration–Negishi coupling route to α,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	^t Bu	64	85
Ph		60	85
Ph	H ₂ C=CH–	59	83
Ph	(<i>E</i>)- ⁿ HexCH=CH–	60	85
Ph	(<i>E</i>)- ⁿ HexCH ₃ C=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.