Synthesis and Palladium-Catalyzed Cross-Coupling of an Alkyl-Substituted Alkenylboronic Acid Pinacol Ester with Aryl Bromides

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https://doi.org/10.33697/ajur.2023.078

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ABSTRACT
The palladium-catalyzed cross-coupling reaction of alkyl-substituted alkenylboron reagents with aryl halides is a versatile method to introduce a hydrophobic hydrocarbon chain onto organic compounds of interest. The application of the cross-coupling reaction is enabled by synthetic methods for the preparation of alkenylboron reagents. The geometrically pure, alkyl-substituted alkenylboron reagent, (*E*)-octenylboronic acid pinacol ester, was prepared by 9-BBN-catalyzed hydroboration reaction of 1-octene with pinacolborane in refluxing 1 M THF solution. This reagent was then evaluated in palladium-catalyzed cross-coupling reactions with aryl bromides. The highest yield of the (*E*)-1-phenyloctene was obtained when SPhos was used as the ligand, K_2CO_3 was used as the base, and DMF was used as the reaction solvent. Other electron-rich, electron-poor, sterically hindered, and heteroaromatic substrates produced the corresponding (*E*)-1-phenyloctene derivatives in moderate to good yield.

KEYWORDS
Organic synthesis; Aryl alkene synthesis; Palladium-catalyzed cross-coupling; Suzuki-Miyaura reaction; Stereocontrolled alkene preparation; Hydroboration; 9-Borobicyclo[3.3.1]nonane; Reaction optimization

INTRODUCTION

Palladium-catalyzed cross-coupling reaction of alkenylboron reagents with aryl halides is a powerful method for the synthesis of stereodefined, organic alkenes.[1-4] It allows for the C-C bond formation between an alkenylboron group with an sp^2-hybridized halide under mildly basic reaction conditions in the presence of a metal catalyst. The low toxicity of alkenylboron groups, the site-selective and stereocontrolled reaction outcomes, and broad functional group tolerance have allowed for ample applications in a variety of synthetic fields.[5] In particular, the cross-coupling reactions of (*E*)-octenylboronic acids and their ester derivatives have drawn considerable attention as efficient methods to introduce a hydrophobic hydrocarbon chain onto organic compounds of interest. For example, Fairlamb *et al.* reported promising antimicrobial activity of 2-pyrone heterocycles substituted with octenyl hydrocarbon chains by cross-coupling reaction of an (*E*)-octenylboronic acid or (*E*)-octenylboronic acid catecol ester.[6] More recently, Suzuki *et al.* evaluated fluorogenic probes bearing (*E*)-octenyl chains introduced by cross-coupling reaction of an (*E*)-octenylboronic acid pinacol ester ((*E*)-**3**).[7] The cross-coupling product was only characterized by high-resolution mass spectrometry, and no optimization of the reaction conditions were reported.

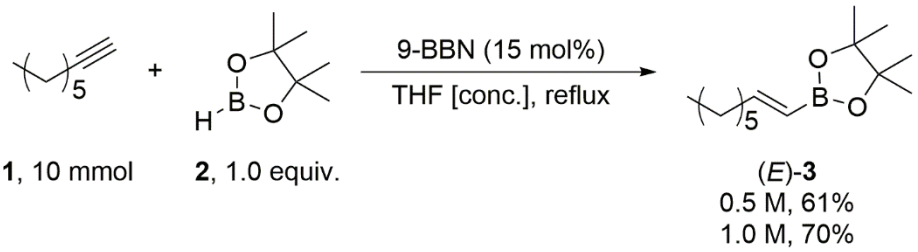
The abundant application of the coupling reaction is enabled by the ease of preparation of alkenylboron reagents.[5] A common preparation method is via hydroboration reaction of an alkyne; the *syn* addition of a boron and hydrogen atom to the carbon-carbon triple bond of an alkyne. Recently, there has been substantial progress in the development of the hydroboration reactions of 1-octyne with pinacolborane catalyzed by transition metal-catalysts[8-13], non-transition metal-catalysts[14-16] and organoboron-catalysts[3,17-19] to prepare the octenylboronic acid pinacol ester. Hoshi *et al.* first reported the synthesis of (*E*)-octenylboronic acid pinacol ester by Cy_2BH catalyzed hydroboration of 1-octyne with pinacolborane in 2004.[20] Thomas and Lloyd-Jones *et al.* elucidated the mechanism of the R_2BH-catalyzed alkyne hydroboration reaction through computational and kinetic approaches.[21]

However, to the best of our knowledge, the preparation of (*E*)-octenylboronic acid pinacol ester by 9-borobicyclo[3.3.1]nonane (9-BBN) catalyzed hydroboration reaction of 1-octyne with pinacolborane has not been reported.

In 2018, we reported the 9-BBN-catalyzed hydroboration reaction of phenylacetylene with pinacolborane.[3] Subsequently, we described the 9-BBN-catalyzed hydroboration reaction of other *para*-substituted, terminal, aryl alkynes with pinacolborane.[22] Our interest in the generality of this reaction led us to the study of alkyl-substituted alkynes in the 9-BBN-catalyzed hydroboration reaction, and the reactivity of the alkenylboronic acid pinacol ester product in subsequent cross-coupling reactions. Here we report the synthesis of (*E*)-octenylboronic acid pinacol ester by 9-BBN-catalyzed hydroboration reaction and its evaluation in palladium-catalyzed cross-coupling reactions with aryl bromides.

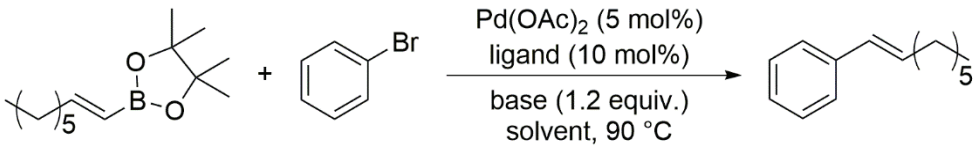
RESULTS AND DISCUSSION

This study began with the preparation of (*E*)-octenylboronic acid pinacol ester by 9-BBN-catalyzed hydroboration reaction of 1-octyne (**1**) with pinacolborane (**2**). Reaction conditions previously used for the 9-BBN-catalyzed hydroboration reaction of phenylacetylene with **2** were initially evaluated with a catalyst loading of 15 mol% and a reaction concentration of 0.5 M.[3] Thus, **1** (10 mmol), **2** (1.0 equiv.), and 9-BBN (15 mol%) were combined and refluxed in 0.5 M THF solution under an atmosphere of argon gas (Scheme 1). The hydroboration reaction of **1** under these conditions produced (*E*)-**3** in 61% yield after purification by aqueous workup and column chromatography. The yield of (*E*)-**3** could be increased to 70% by increasing the reaction concentration from 0.5 M to 1.0 M.



Scheme 1. Synthesis of (*E*)-**3** by 9-BBN-catalyzed hydroboration of 1-octene with pinacolborane.

The evaluation of the reaction conditions for the palladium-catalyzed cross-coupling reaction of (*E*)-**3** with bromobenzene **4a** was then investigated (Table 1). These experiments began with the use of reaction conditions previously published for the palladium-catalyzed cross-coupling reaction of (*E*)-2-phenylethenylboronic acid pinacol ester with aryl bromides.[3] Thus, (*E*)-**3** (1.2 equiv.), **2** (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), *t*-Bu_3PHBF_4 (10 mol%), K_2CO_3 (1.2 equiv), and DMF were combined and heated to 90 °C under an atmosphere of argon gas. These conditions produced (*E*)-**5a** in 52% isolated yield. The ligands JohnPhos, DPPF, Ph_3P, and SPhos were then evaluated in efforts to increase the yield of (*E*)-**5a** (entries 1-5). Of these ligands, the use of the SPhos ligand produced (*E*)-**5a** in the highest yield (entry 5). Dioxane was evaluated as the reaction solvent in reactions that employed both Ph_3P and SPhos as ligands (entries 6 and 7). The use of DMF as the solvent was found to provide a better yield in both of these reactions. A lower yield of (*E*)-**5a** was observed when *t*-BuOK or NaOH were used as the base instead of K_2CO_3 (entries 5, 8 and 9).



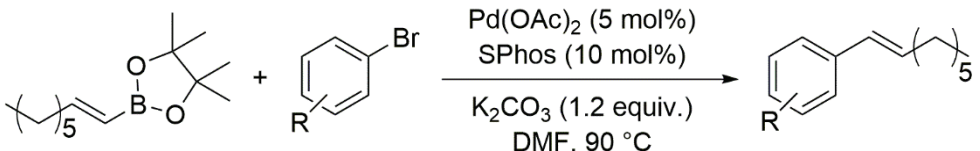
(*E*)-**3**, 1.2 equiv. **4a**, 1.0 equiv. (*E*)-**5a**

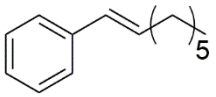
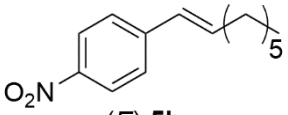
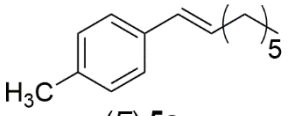
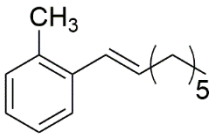
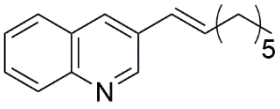
Entry	Ligand	Base	Solvent	Yield,[b] %
1	*t*-Bu_3PhBF_4	K_2CO_3	DMF	52
2	JohnPhos	K_2CO_3	DMF	69
3	DPPF	K_2CO_3	DMF	73
4	Ph_3P	K_2CO_3	DMF	71
5	SPhos	K_2CO_3	DMF	77
6	Ph_3P	K_2CO_3	Dioxane	73
7	SPhos	K_2CO_3	Dioxane	65
8	SPhos	*t*-BuOK	DMF	61
9	SPhos	NaOH	DMF	59

[a]Reactions were performed on >0.5 mmol scale.
[b]Yield of isolated, purified product.

Table 1. Optimization of the palladium-catalyzed cross-coupling reaction of (*E*)-**3** and **4a**.[a]

The optimized reaction conditions of (*E*)-**3** (1.2 equiv), aryl bromide (1.0 equiv.), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_2CO_3 (1.2 equiv), DMF at 90 °C were then used to evaluate the scope of compatible aryl bromides (Table 2). The electronically neutral substrate bromobenzene (**4a**) provided the product (*E*)-**5a** in the highest isolated yield (entry 1). The substrate 1-bromo-4-nitrobenzene (**4b**) that bears an electron-withdrawing group provided a good yield of the product (*E*)-**5b**. The substrate 4-bromotoluene (**4c**) that bears an electron-donating group provided the lowest yield of the product (*E*)-**5c** (entry 3). Interestingly, the sterically hindered *o*-substituted aryl bromide 2-bromotoluene (**4d**) provided the product (*E*)-**5d** in a higher yield than the less sterically hindered *p*-substituted aryl bromide (entries 3 and 4). This is noteworthy because sterically hindered substrates are typically challenging substrates in palladium-catalyzed cross-coupling reactions.[23,24] The heterocyclic aryl bromide 3-bromoquinoline (**4e**) that bears a Lewis basic nitrogen atom provided the product (*E*)-**5e** in a good yield (entry 5).



Entry	Product	Yield,[b] %
1	 (*E*)-**5a**	77
2	 (*E*)-**5b**	62
3	 (*E*)-**5c**	36
4	 (*E*)-**5d**	68
5	 (*E*)-**5e**	60

[a]Reactions were performed in duplicate on >0.5 mmol scale.
[b]Yield of isolated, purified product.

Table 2. Aryl bromides evaluated in the synthesis of 1-phenyloctene derivatives by palladium-catalyzed cross-coupling reaction.[a]

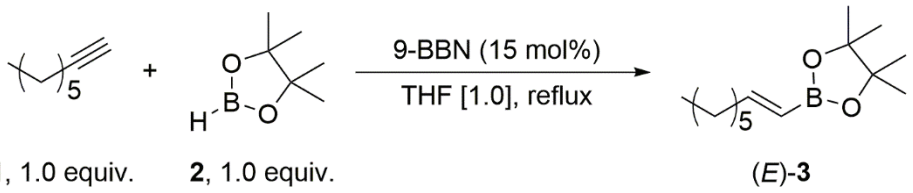
METHODS AND PROCEDURES

General Hydroboration Procedure: An oven-dried, round-bottom flask, containing a magnetic stir-bar, equipped with an oven-dried Liebig condenser was sealed with high-vacuum grease. The reflux apparatus was capped with a septum and purged with argon under a balloon of argon. The followings were added sequentially by syringe: the solvent, 1-octyne, pinacolborane, 9-BBN, and an additional volume of solvent to wash all of the reagents into the flask. The reaction solution was refluxed in a preheated oil bath at 65 °C. Reaction aliquots were analyzed by thin-layer chromatography (TLC) to monitor the progress of the reaction. When the reaction was determined to be complete, it was cooled to room temperature, extracted with ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated by rotary evaporation (50 °C, 70 torr). The crude product was purified by flash chromatography on silica. The amount of silica used in the chromatography was approximately 50 times the mass of the concentrated crude product. The composition of the eluent began at 97.5:2.5, hexane/ethyl acetate and the polarity of

the eluent was gradually increased to 90:10, hexane/ethyl acetate until the product was completely eluted. The product was concentrated *in vacuo* (2 torr) to afford the desired product.

General Cross-Coupling Procedure: To an oven-dried, round-bottom flask, containing a magnetic stir-bar was added (*E*)-**3a**, aryl bromide, base, ligand, and $Pd(OAc)_2$. The flask was capped with a septum and purged with argon under a balloon of argon. The solvent was then added by syringe. The reaction solution was stirred under a balloon of argon in a preheated oil bath at 90 °C. Reaction aliquots were analyzed by TLC to monitor the progress of the reaction. When the reaction was determined to be complete, it was cooled to room temperature, extracted with ethyl acetate, washed with water, brine, dried with sodium sulfate, filtered and concentrated by rotary evaporation (50 °C, 70 torr). The crude product was purified by flash chromatography on silica. The amount of silica used in the chromatography was approximately 50 times the mass of the concentrated crude product. Elution began with hexane and the polarity of the eluent was gradually increased to 95:5, hexane/ethyl acetate until the product was completely eluted. The product was concentrated in vacuo (2 torr) to afford the desired product.

Procedure for the synthesis of *4,4,5,5-Tetramethyl-2-(1E)-1-octen-1-yl-1,3,2-dioxaborolane* ((*E*)-**3**)



Scheme 2. Synthesis of (*E*)-**3** by 9-BBN-catalyzed hydroboration of **1** with **2**.

Following the General Hydroboration Reaction Procedure, 1-octyne (1.54 mL, 10 mmol, 1.0 equiv), pinacolborane (1.45 mL, 10 mmol, 1.0 equiv), 9-BBN (3.0 mL, [0.5], 1.5 mmol, 0.1 equiv.), and THF (10 mL) were combined and heated to 65 °C for 1.25 h. Purification by aqueous workup and flash chromatography afforded 1.678 g (70%) of (*E*)-**3** as a clear, colorless oil.[25]

Data for *4,4,5,5-Tetramethyl-2-(1E)-1-octen-1-yl-1,3,2-dioxaborolane* ((*E*)-**3**)

^{1}H NMR: (400 MHz, $CDCl_3$)
6.63 (dt, *J* = 17.9 & 7.4 Hz, 1H), 5.42 (dt, *J* = 17.9 & 1.6 Hz, 1H), 2.17-2.11 (m, 2H), 1.43-1.37 (m, 2H), 1.27-1.24 (m, 18H), 0.89-0.85 (m, 3H).

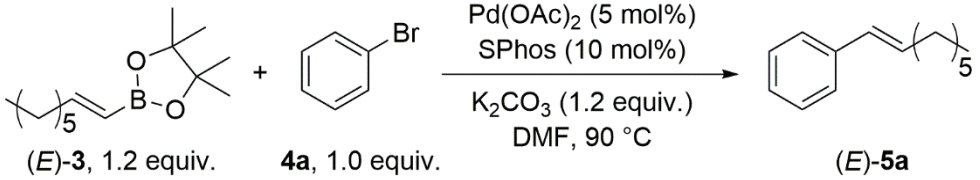
^{13}C NMR: (101 MHz, $CDCl_3$)
154.8, 83.0, 35.8, 31.7, 28.9, 28.2, 24.8, 22.6, 14.10.

IR: (neat)
2977 (w), 2924 (m), 2855 (w), 2179 (w), 1743 (w), 1638 (m), 1467 (w), 1398 (w), 1360 (m), 1388 (s), 1316 (s), 1269 (w), 1215 (w), 1145 (s), 1047 (w), 997 (m), 970 (m), 900 (w), 849 (m), 724 (w), 646 (w), 577 (w), 522 (w).

MS: (EI, 70 eV)
238 ($[M]^+$, 1), 223 ($[M\text{-}CH_3]^+$, 28), 222 (7), 181 (7), 168 (5), 154 (21), 153 (100), 152 (47), 140 (14), 139 (66), 138 (26), 137 (8), 125 (10), 124 (8), 123 (9), 112 (9), 111 (38), 110 (48), 109 (27), 101 (34), 98 (5), 97 (20), 96 (33), 95 (42), 94 (7), 87 (5), 86 (6), 85 (77), 84 (60), 83 (61), 82 (36), 81 (45), 80 (7), 79 (9), 71 (10), 70 (10), 69 (67), 68 (73), 67 (55), 66 (8), 65 (5), 59 (43), 58 (11), 57 (47), 56 (16), 55 (96), 54 (96), 53 (17).

TLC: R_f 0.63 (hexane/ethyl acetate, 90:10) [silica gel, I_2]

Procedure for the synthesis of *(1E)-1-Octen-1-ylbenzene* ((*E*)-**5a**)



Scheme 3. Synthesis of (*E*)-**5a** by palladium-catalyzed cross-coupling of (*E*)-**3** with **4a**.

Following the General Cross-Coupling Procedure, (*E*)-**3** (190 mg, 0.8 mmol, 1.2 equiv.), bromobenzene (70 µl , 0.67 mmol, 1.0 equiv), K_2CO_3 (110 mg, 0.80 mmol, 1.2 equiv.), $Pd(OAc)_2$ (7.4 mg, 0.033 mmol, 0.05 equiv.), SPhos (27 mg, 0.067 mmol, 0.1 equiv), and DMF (3.3 mL) were combined and heated to 90°C for 3 h. Purification by aqueous workup and flash chromatography afforded 96 mg (77 %) of (*E*)-**5a** as a clear oil.[26]

Data for *(1E)-1-Octen-1-ylbenzene* ((*E*)-**5a**)

^{1}H NMR: (400 MHz, $CDCl_3$)
7.36-7.26 (m, 4H), 7.21-7.16 (m, 1H), 6.37 (appd, J = 15.8 Hz, 1H), 6.23 (dt, J = 15.8 & 6.8 Hz, 1H), 2.24-2.17 (m, 2H), 1.51-1.43 (m, 2H), 1.39-1.28 (m, 6H), 0.91-0.88 (m, 3H).

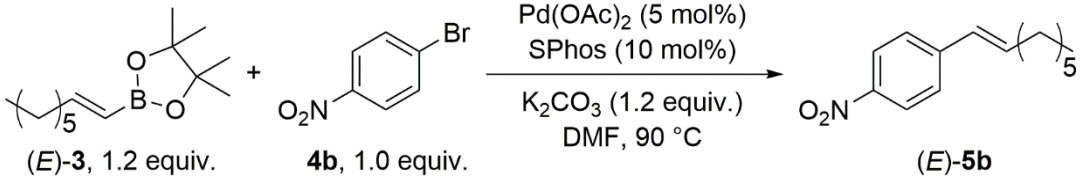
^{13}C NMR: (101 MHz, $CDCl_3$)
138.0, 131.3, 129.6, 128.4, 126.7, 125.9, 33.0, 31.8, 29.3, 28.9, 22.6, 14.1.

IR: (neat)
3023 (w), 2953 (w), 2922 (m), 2851 (m), 2190 (w), 1994 (w), 1917 (w), 1737 (s), 1596 (w), 1492 (w), 1447 (m), 1365(m), 1228 (m), 1216 (m), 1070 (w), 1028 (w), 961 (m), 907(w), 740 (w), 690 (m), 527 (w).

MS: (EI, 70 eV)
188 ([M]$^+$, 32), 129 (6), 118 (14), 117 ([M-$(CH_2)_4CH_3$]$^+$, 100), 116 (12), 115 (41), 105 (9), 104 (92), 91 (31).

TLC: R_f 0.80 (hexane/ethyl acetate, 90:10) [silica gel, UV light and I_2]

Procedure for the synthesis of *1-Nitro-4-(1E)-1-octen-1-ylbenzene* ((*E*)-**5b**)



Scheme 4. Synthesis of (*E*)-**5b** by palladium-catalyzed cross-coupling of (*E*)-**3** with **4b**.

Following the General Cross-Coupling Procedure, (*E*)-**3** (213 mg, 0.89 mmol, 1.2 equiv.), 1-bromo-4-nitrobenzene (149 mg, 0.74 mmol, 1.0 equiv), K_2CO_3 (123 mg, 0.89 mmol, 1.2 equiv.), $Pd(OAc)_2$ (8.2 mg, 0.047 mmol, 0.05 equiv.), SPhos (30 mg, 0.074 mmol, 0.1 equiv), and DMF (3.7 mL) were combined and heated to 90°C for 3.5h. Purification by aqueous workup and flash chromatography afforded 107 mg (62%) of (*E*)-**5b** as a yellow oil.[27]

Data for *1-Nitro-4-(1E)-1-octen-1-ylbenzene* ((*E*)-**5b**)

^{1}H NMR: (400 MHz, $CDCl_3$)
8.17-8.14 (m, 2H), 7.47-7.43 (m, 2H), 6.45-6.43 (m, 2H), 2.29-2.24 (m, 2H), 1.53-1.46 (m, 2H), 1.39-1.28 (m, 6H), 0.91-0.88 (m, 3H).

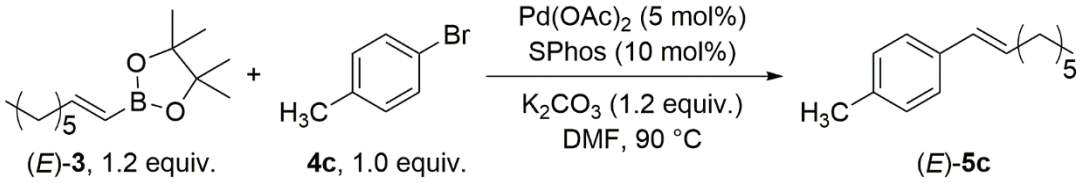
^{13}C NMR: (101 MHz, $CDCl_3$)
146.4, 144.5, 136.7, 128.1, 126.3, 124.0, 33.2, 31.7, 28.94, 28.90, 22.6, 14.1.

IR: (neat)
2968 (w), 2953 (m), 2924 (m), 2189 (w), 2163 (w), 2117 (w), 2018 (w), 1737 (m), 1647 (w), 1594 (m), 1512 (s), 1455 (w), 1374 (w), 1339 (s), 1228 (m), 1216 (m), 1205 (m), 1180 (w), 1108 (m), 1010 (w), 966 (m), 954 (m), 859 (m), 822 (w), 743 (m), 689 (w), 665 (w), 630 (w), 537 (w), 527 (w).

MS: (EI, 70 eV)
233 ([M]$^+$, 13), 150 (17), 149 (100), 137 (14), 129 (7), 128 (10), 119 (14), 117 (11), 116 (57), 115 (48), 103 (7), 91 (9), 55 (12).

TLC: R_f 0.74 (hexane/ethyl acetate, 90:10) [silica gel, UV light and I_2]

Procedure for the synthesis of *1-Methyl-4-(1E)-1-octen-1-ylbenzene* ((*E*)-**5c**)



Scheme 5. Synthesis of (*E*)-**5c** by palladium-catalyzed cross-coupling of (*E*)-**3** with **4c**.

Following the General Cross-Coupling Procedure, (*E*)-**3** (180 mg, 0.76 mmol, 1.2 equiv.), 4-bromotoluene (77 µl , 0.63 mmol, 1.0 equiv), K_2CO_3 (104 mg, 0.76 mmol, 1.2 equiv.), $Pd(OAc)_2$ (7.0 mg, 0.032 mmol, 0.05 equiv.), SPhos (26 mg, 0.063 mmol, 0.1 equiv), and DMF (3.2 mL) were combined and heated to 90 °C for 17 hr. Purification by aqueous workup and flash chromatography afforded 46 mg (36 %) of (*E*)-**5c** as a clear oil.[28]

Data for *1-Methyl-4-(1E)-1-octen-1-ylbenzene* ((*E*)-**5c**)

^{1}H NMR: (400 MHz, $CDCl_3$)
7.24-7.23 (m, 2H), 7.11-7.09 (m, 2H), 6.34 (appd, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.8 & 6.9 Hz, 1H), 2.32 (s, 3H), 2.22-2.16 (m, 2H), 1.49-1.42 (m, 2H), 1.37-1.27 (m, 6H), 0.91-0.87 (m, 3H).

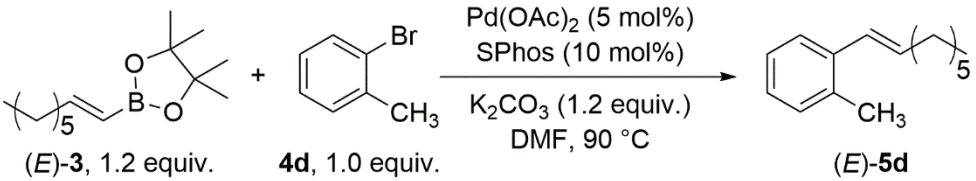
^{13}C NMR: (101 MHz, $CDCl_3$)
136.4, 135.2, 130.2, 129.5, 129.1, 125.8, 33.0, 31.7, 29.4, 28.9, 22.6, 21.1, 14.1.

IR: (neat)
3020 (w), 2954 (m), 2921 (m), 2852 (m), 2293 (w), 1987 (w), 1844 (w), 1690 (w), 1628 (w), 1511 (m), 1455 (m), 1376 (w), 1229 (w), 1204 (w), 1197 (w), 1105 (w), 1101 (w), 962 (s), 837 (m), 787 (m), 723 (m), 516 (w), 502 (w).

MS: (EI, 70 eV)
202 ($[M]^+$, 28), 132 (11), 131 ($[M-(CH_2)_4CH_3]^+$, 100), 129 (13), 128 (9), 118 (43), 117 (12), 116 (14), 115 (17), 111 (6), 105 (13), 97 (9), 91 (16), 85 (100, 83 (9), 71 (15), 70 (7), 69 (10), 57 (20), 55(12).

TLC: R_f 0.82 (hexane/ethyl acetate, 90:10) [silica gel, UV light and I_2]

Procedure for the synthesis of *1-Methyl-2-(1E)-1-octen-1-ylbenzen*e ((*E*)-**5d**)



Scheme 6. Synthesis of (*E*)-**5d** by palladium-catalyzed cross-coupling of (*E*)-**3** with **4d**.

Following the General Cross-Coupling Procedure, (*E*)-**3** (172 mg, 0.72 mmol, 1.2 equiv.), 2-bromotoluene (72 µl , 0.60 mmol, 1.0 equiv), K_2CO_3 (99 mg, 0.72 mmol, 1.2 equiv.), $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 0.05 equiv.), SPhos (25 mg, 0.060 mmol, 0.1 equiv), and DMF (3.0 mL) were combined and heated to 90 °C for 17.5 hr. Purification by aqueous workup and flash chromatography afforded 83 mg (68 %) of (E)-**5d** as a clear oil.[27]

Data for *1-Methyl-2-(1E)-1-octen-1-ylbenzen*e ((*E*)-**5d**)

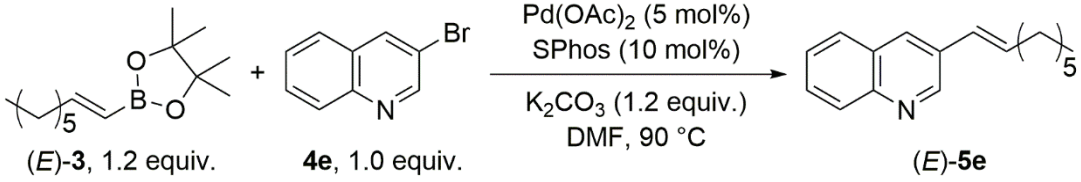
^{1}H NMR: (400 MHz, $CDCl_3$)
7.43-7.41 (m, 1H), 7.18-7.11 (m, 3H), 6.58 (appd, *J* = 15.6 Hz, 1H), 6.10 (dt, *J* = 15.6 & 7.0 Hz, 1H), 2.34 (s, 3H), 2.27-2.21 (m, 2H), 1.54-1.45 (m, 2H), 1.41-1.30 (m, 6H), 0.93-0.89 (m, 3H).

^{13}C NMR: (101 MHz, $CDCl_3$)
137.1, 134.8, 132.6, 130.1, 127.5, 126.7, 126.0, 125.4, 33.3, 31.7, 29.4, 28.9, 22.6, 19.8, 14.1.

IR: (neat)
3016 (w), 2953 (w), 2922 (m), 2852 (w), 2015 (w), 2007 (w), 1954 (w), 1887 (w), 1737 (m), 1647 (w), 1600 (w), 1483 (w), 1457 (m), 1376 (m), 1228 (m), 1216 (m), 1032 (w), 963 (m), 742 (m), 527 (w).

MS: (EI, 70 eV)
202 ([M]$^+$, 33), 132 (13), 131 ([M-$(CH_2)_4CH_3$]$^+$, 100), 129 (16), 128 (12), 119 (8), 118 (57), 117 (24), 116 (20), 115 (25), 111 (7), 105 (19), 97 (11), 91 (22), 85 (12), 83 (10), 71 (17).
TLC: R_f 0.81 (hexane/ethyl acetate, 90:10) [silica gel, UV light, and I_2]

Procedure for the synthesis of *3-(1E)-1-Octen-1-ylquinoline* ((*E*)-**5e**)



Scheme 7. Synthesis of (*E*)-**5e** by palladium-catalyzed cross-coupling of (*E*)-**3** with **4e**.

Following the General Cross-Coupling Procedure, (*E*)-**3** (211 mg, 0.89 mmol, 1.2 equiv.), 3-bromoquinoline (100 µl , 0.74 mmol, 1.0 equiv), K_2CO_3 (122 mg, 0.89 mmol, 1.2 equiv.), $Pd(OAc)_2$ (8.3 mg, 0.037 mmol, 0.05 equiv.), SPhos (30 mg, 0.074 mmol, 0.1 equiv), and DMF (3.7 mL) were combined and heated to 90°C for 2 hr. Purification by aqueous workup and flash chromatography afforded 107 mg (60 %) of (*E*)-**5e** as a clear oil.[29]

Data for *3-(1E)-1-Octen-1-ylquinoline* ((*E*)-**5e**)
^{1}H NMR: (400 MHz, $CDCl_3$)
8.971-8.966 (m, 1H), 8.08-8.06 (m, 1H), 7.997-7.992 (m, 1H), 7.78-7.76 (m, 1H), 7.67-7.62 (m, 1H), 7.53-7.49 (m, 1H), 6.53 (appd, *J* = 16.1 Hz, 1H), 6.50-6.43 (m, 1H), 2.31-2.26 (m, 2H), 1.56-1.48 (m, 2H), 1.41-1.30 (m, 6H) 0.92-0.89 (m, 3H).
^{13}C NMR: (101 MHz, $CDCl_3$)
149.0, 146.7, 134.3, 131.8, 130.8, 128.92, 128.88, 128.2, 127.7, 126.9, 126.4, 33.3, 31.7, 29.1, 28.9, 22.6, 14.1.
IR: 3129 (w), 3099 (w), 3078 (w), 2952 (w), 2921 (m), 2851 (m), 2088 (w), 2075 (w), 2052 (w), 1649 (w), 1567 (w), 1490 (m), 1464 (m), 1374 (w), 1339 (w), 1295 (w), 1204 (w), 1189 (w), 1122 (w), 1015 (w), 962 (s), 906 (m), 858 (w), 783 (m), 748 (s), 616 (w).
MS: (EI, 70 eV)
240 ([M+1]$^+$, 7), 239 ([M]$^+$, 37), 182 (7), 180 (9), 169 (15), 168 ([M-$(CH_2)_4CH_3$]$^+$, 100), 167 (61), 166 (8), 157 (9), 156 (21), 155 (50), 154 (8), 143 (15), 142 (7), 115 (8).
TLC: R_f 0.31 (hexane/ethyl acetate, 90:10) [silica gel, UV light and I_2]

CONCLUSION

A hydrophobic octenyl chain can be introduced to aromatic bromides by palladium-catalyzed cross-coupling reaction of (*E*)-**3** with aryl bromides. The geometrically pure reagent (*E*)-**3** can be prepared by the 9-BBN-catalyzed hydroboration reaction of **1** with **2** in refluxing 1 M THF solution. The alkyl-substituted alkenylboronic acid reagent (*E*)-**3** undergoes efficient cross-coupling with aryl bromides under palladium catalysis to provide the desired products (*E*)-**5a-e** in moderate to good yield. The highest reaction yield was obtained when SPhos was used as the ligand, K_2CO_3 was used as the base, and DMF was used as the reaction solvent. We intend to continue to explore the 9-BBN-catalyzed hydroboration reaction and the palladium-catalyzed cross-coupling reaction of the alkenylboronic acid pinacol ester products.

ACKNOWLEDGEMENTS

We are grateful to Organic Syntheses Inc. for a Summer Research at an Undergraduate Institution Grant (N.S.W.), and Southern Utah University for a Walter Maxwell Gibson Research Fellowship (S.M.) and L. S. and Aline W. Skaggs Research Grant (S.M.) to generously support this work. We are grateful to Maddelyn Lunt for providing characterization data for (*E*)-**3**.

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PRESS SUMMARY

The palladium-catalyzed cross-coupling reaction is a versatile method to introduce a hydrophobic, water-fearing, hydrocarbon chain onto a variety of organic compounds of interest to science and medicine. In this work, a reagent was prepared with a hydrophobic hydrocarbon chain and was shown to undergo a cross-coupling reaction with aryl bromides under palladium-catalysis. The reaction conditions for the carbon-carbon bond forming, cross-coupling reaction were optimized to achieve a high yield of the product. A variety of reaction partners were shown to undergo this site-selective and stereocontrolled chemical reaction.