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Palladium(0)-Catalyzed Highly Regio- and Stereoselective Addition of Organoboronic Acids with 1,2-Allenylphosphonates Forming Tri- or Tetrasubstituted 1(*E*)-Alkenylphosphonates

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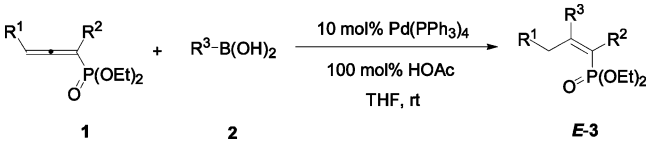
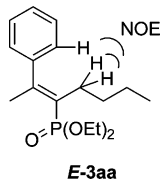


A highly regio- and stereoselective palladium(0)-catalyzed addition of organoboronic acids with 1,2-allenylphosphonates in the presence of HOAc forming tri- or tetrasubstituted 1(*E*)-alkenylphosphonates is reported in this paper. The stereoselectivity is much higher than the reported cases. The effects of different R^1, R^2, and R^3 were studied. A mechanism of this reaction is proposed on the basis of our previous study.

Organoboronic acids are very important and useful reagents in organic synthesis.[1] One of the most notable reactions is their palladium-catalyzed cross-coupling reaction with organic halides (the Suzuki couple reaction).[2] Another important application is the rhodium- or nickel-catalyzed conjugate additions[3] of organoboronic acids to electron-deficient C−C double or triple bonds,[4−6] C═O bonds (aldehydes),[7] and C═N bonds (*N*-sulfonylimines).[8] Transition metal-catalyzed addition reactions of organoboronic acids to electron-rich carbon−carbon double or triple bonds are rare.[9] Recently, Oh et al. reported the Pd-catalyzed addition reaction of alkynes with organoboronic acids affording trisubstituted alkenes stereoselectively.[9] We and Oh et al. reported the Pd-catalyzed reaction of allenes with organoboronic acids in the presence of HOAc.[10−12] However, the regio- and stereoselectivity or yield is not excellent. On the other hand, phosphonates show very important bioactivities,[13] and 1-alkenylphosphonates are important intermediates in organic synthesis,[14] so highly stereoselective methods for the synthesis of substituted 1-alkenylphosphonates are desirable. Here, we wish to report a highly regio- and stereoselective palladium(0)-catalyzed addition of organoboronic acids with 1,2-allenyl phosphonates in the presence of HOAc forming tri- or tetrasubstituted 1(*E*)-alkenyl phosphonates.



E-**3aa**

FIGURE 1. $^1H-^1H$ NOESY of *E*-**3aa**.

The solvent effect of the addition reaction of 1,2-allenyl phosphonate **1a** with phenylboronic acid **2a** was studied first (Table 1). In $MeNO_2$, dioxane, ether, MeCN, and toluene, no reaction was observed (entries 1−5, Table 1). In MeOH, however, two regioisomeric products *E*-**3aa** and **4aa** were formed in 75% combined yield with a ratio of 85:15 (entry 6, Table 1). The configuration of the C═C bond in **3aa** was determined by the $^1H-^1H$ NOESY spectrum (Figure 1). The reaction in DMF and CH_2Cl_2 is highly regio- and stereoselective, but the yield is rather poor (entries 7 and 8, Table 1). Best results were obtained when the reaction was conducted in THF (entry 9, Table 1). Under this set of standard reaction conditions, the reaction afforded *E*-**3aa** as the only product highly selectively in good yield.

We also tried other palladium catalysts with some of the typical results shown in Table 2. No better results were observed; thus, $Pd(PPh_3)_4$ was chosen as the catalyst for this reaction.

The effects of the loading of $Pd(PPh_3)_4$ and the temperature were then examined carefully (Table 3). The results indicated

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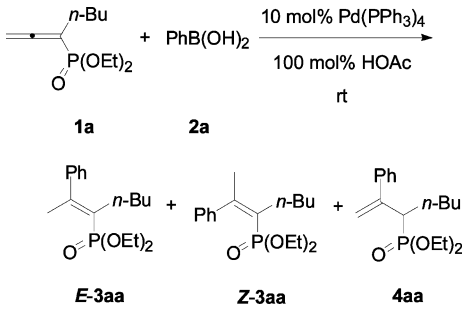
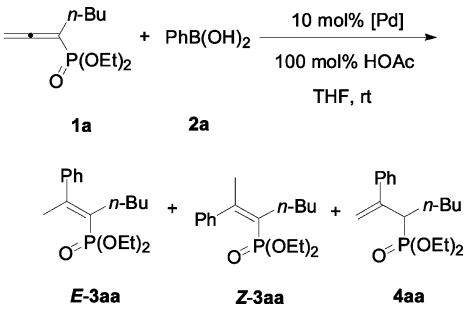
TABLE 1. Pd(0)-Catalyzed Addition of 1,2-Allenylphosphonate 1a with Phenylboronic Acid 2a in Different Solvents[a]



entry	solvent	time (h)	isolated yield of **3aa** + **4aa** (%)	*E*-**3aa**/*Z*-**3aa**/**4aa**[b]
1	CH_3NO_2	41	trace	
2	dioxane	72	NR (53% of **1a** was recovered)	
3	ether	72	NR (71% of **1a** was recovered)	
4	CH_3CN	72	NR (38% of **1a** was recovered)	
5	toluene	72	NR (48% of **1a** was recovered)	
6	CH_3OH	41	75	85:0:15
7	DMF	72	12	≥97% of *E*-**3aa**[c]
8	CH_2Cl_2	24	23	≥97% of *E*-**3aa**[c]
9	THF	24	81	≥97% of *E*-**3aa**[c]

[a] The reaction was carried out at rt using **1a** (0.25 mmol), **2a** (0.5 mmol), $Pd(PPh_3)_4$ (10 mol %), and HOAc (100 mol %) in 3 mL of solvent under nitrogen atmosphere. [b] Determined by 300 MHz ^{1}H NMR analysis. [c] *Z*-**3aa** and **4aa** were not observed in the crude NMR spectra. Due to the accuracy of the 300 MHz ^{1}H NMR spectrometer, it was assumed that the selectivity for *E*-**3aa** was ≥97%.

TABLE 2. Pd(0)-Catalyzed Addition of 1,2-Allenylphosphonate 1a with Phenylboronic Acid 2a in THF Using Different Catalysts[a]

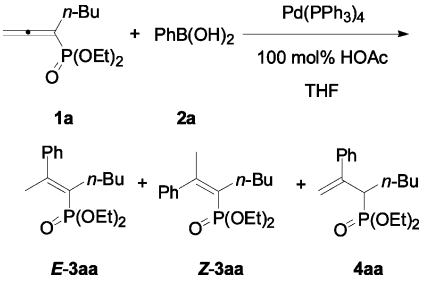


entry	catalyst	time (h)	isolated yield of **3aa** + **4aa** (%)	*E*-**3aa**/*Z*-**3aa**/**4aa**[b]
1	$Pd(OAc)_2$	45	trace	
2	$PdCl_2$	72	NR (53% of **1a** was recovered)	
3[c]	$PdCl_2$	72	NR (36% of **1a** was recovered)	
4[c]	$Pd(PhCN)_2Cl_2$	72	NR (21% of **1a** was recovered)	
5[c]	$Pd(dba)_2$	45	70	≥97% of *E*-**3aa**[d]
6[c]	$Pd(OAc)_2$	45	57	≥97% of *E*-**3aa**[d]

[a] The reaction was carried out at rt using **1a** (0.25 mmol), **2a** (0.5 mmol), [Pd] (10 mol %), and HOAc (100 mol %) in 3 mL of THF under nitrogen atmosphere. [b] Determined by 300 MHz ^{1}H NMR analysis. [c] 20 mol % of PPh_3 was applied. [d] See footnote *c* of Table 1.

that 10 mol % of $Pd(PPh_3)_4$ and rt are required for this reaction (entry 4, Table 3).

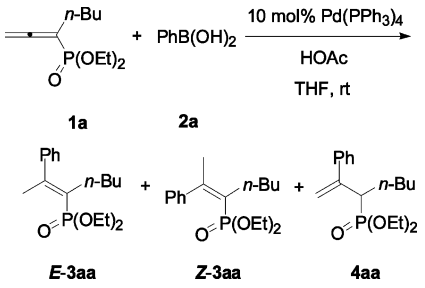
TABLE 3. Pd(0)-Catalyzed Addition of 1,2-Allenylphosphonate 1a with Phenyl Boronic Acid 2a in THF at Different Reaction Temperature Using Different Amounts of $Pd(PPh_3)_4$[a]



entry	$Pd(PPh_3)_4$ (mol %)	*T* (°C)	time (h)	isolated yield of **3aa** + **4aa** (%)	*E*-**3aa**/*Z*-**3aa**/**4aa**[b]
1	1	rt	91	NR[c]	
2	3	rt	91	71	98:0:2
3	5	rt	91	75	98:0:2
4	10	rt	24	81	≥97% of *E*-**3aa**[d]
5	5	50	33	66	≥97% of *E*-**3aa**[d]
6	5	reflux	33	66	≥97% of *E*-**3aa**[d]
7	10	50	9	65	≥97% of *E*-**3aa**[d]
8	10	reflux	9	63	≥97% of *E*-**3aa**[d]

[a] The reaction was carried out using **1a** (0.25 mmol), **2a** (0.5 mmol), and HOAc (100 mol %) in 3 mL of THF under nitrogen atmosphere. [b] Determined by 300 MHz ^{1}H NMR analysis. [c] 69% of **1a** was recovered. [d] See footnote *c* of Table 1.

TABLE 4. Pd(0)-Catalyzed Addition of 1,2-Allenylphosphonate 1a with Phenylboronic Acid 2a at Room Temperature in THF Using Different Amounts of HOAc[a]



entry	HOAc (mol %)	time (h)	isolated yield of **3aa** + **4aa** (%)	*E*-**3aa**/*Z*-**3aa**/**4aa**[b]
1	20	48	56	≥97% of *E*-**3aa**[c]
2	50	35	66	≥97% of *E*-**3aa**[c]
3	100	24	81	≥97% of *E*-**3aa**[c]
4	200	23	75	≥97% of *E*-**3aa**[c]

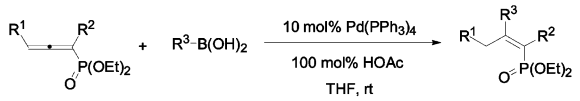
[a] The reaction was carried out at rt using **1a** (0.25 mmol), **2a** (0.5 mmol), HOAc, and $Pd(PPh_3)_4$ (10 mol %) in 3 mL of THF under nitrogen atmosphere. [b] Determined by 300 MHz ^{1}H NMR analysis. [c] See footnote *c* of Table 1.

We also tried the reaction in the presence of different amounts of HOAc (Table 4). The best result was observed with 100 mol % of HOAc (entry 3, Table 4).

Thus, conditions A (10 mol % of $Pd(PPh_3)_4$, 100 mol % of HOAc, THF, and rt) was applied for the highly regio- and stereoselective addition of organoboronic acids with different 1,2-allenyl phosphonates affording tri- or tetrasubstituted 1(*E*)-alkenyl phosphonates.

At first, we investigated the reaction of different 1,2-allenyl phosphonates **1a**−**f** with *p*-methylphenylboronic acid **2b** (entries 1−6, Table 5). All of the reactions afforded 1(*E*)-alkenyl phosphonates *E*-**3** as the only product. Then, we investigated

TABLE 5. Pd(0)-Catalyzed Addition of 1,2-Allenylphosphonates 1a−f with Organoboronic Acids 2b−h under Conditions A



1 2 *E*-3

Entry	1 R¹ / R²	2 R³	Time (h)	Isolated Yield of *E*-3 (%)
1	H / *n*-Bu (**1a**)	*p*-MeC$_6$H$_4$ (**2b**)	52	90 (***E*-3ab**)
2	H / H (**1b**)	*p*-MeC$_6$H$_4$ (**2b**)	47	87 (***E*-3bb**)
3	H / Me (**1c**)	*p*-MeC$_6$H$_4$ (**2b**)	77	85 (***E*-3cb**)
4	H / *n*-C$_7$H$_{15}$ (**1d**)	*p*-MeC$_6$H$_4$ (**2b**)	76	91 (***E*-3db**)
5	H / Ph (**1e**)	*p*-MeC$_6$H$_4$ (**2b**)	135	47 (***E*-3eb**)
6	*n*-Bu / H (**1f**)	*p*-MeC$_6$H$_4$ (**2b**)	34	52 (***E*-3fb**)[a]
7	H / *n*-Bu (**1a**)	*m*-MeOC$_6$H$_4$ (**2c**)	70	91 (***E*-3ac**)
8	H / *n*-Bu (**1a**)	*p*-MeOC$_6$H$_4$ (**2d**)	65	88 (***E*-3ad**)
9	H / *n*-Bu (**1a**)	*p*-MeCOC$_6$H$_4$(**2e**)	65	85 (***E*-3ae**)
10	H / *n*-Bu (**1a**)	*m*-NO$_2$C$_6$H$_4$ (**2f**)	32	81 (***E*-3af**)
11	H / *n*-Bu (**1a**)	1-(*E*)-heptenyl (**2g**)	96	89 (***E,E*-3ag**)
12	H / *n*-Bu (**1a**)	PhOCH$_2$ (**2h**)	78	71 (***E,E*-3ah**)

[a] The formation of another unidentified product was observed.

the reaction of 1,2-allenyl phosphonate **1a** with different organoboronic acids **2c**−**h** with the typical results listed in Table 5 (entries 7−12, Table 5): Both electron-donating and -withdrawing groups can be installed to the phenyl ring of the arylboronic acids **2c**−**f** (entries 7−10, Table 5); 1-alkenylboronic acids **2g** and **2h** behaved similarly (entries 11 and 12, Table 5). In all cases, the formation of *Z*-**3** was not observed as determined by the 300 MHz ^{1}H NMR analysis of the crude reaction products.

According to our previous ESI-MS study,[12] this reaction may also proceed via the oxidative addition of HOAc and Pd(0), which was followed by regioselective hydrometalation of the terminal C═C bond in **1** forming sp^2-C−Pd species. Subsequent Suzuki-type coupling of the sp^2-C−Pd species with organoboronic acid **2** afforded *E*-**3** highly stereoselectively.

We have demonstrated the highly regio- and stereoselective palladium(0)-catalyzed addition of organoboronic acids with 1,2-allenylphosphonates in the presence of HOAc forming tri- or tetrasubstituted 1(*E*)-alkenylphosphonates. Further studies in this area and the synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

Diethyl (Hepta-1,2-dien-3-yl)phosphonate (1a). Typical Procedure I.[15] To a solution of hept-2-yn-1-ol (1.152 g, 10 mmol), Et$_3$N (1.5 mL, 11 mmol), and THF (25 mL) was added a solution of P(OEt)$_2$Cl (2.093 g, 13 mmol) in THF (5 mL) dropwise at −78 °C. After the addition, the resulting mixture was heated under reflux. After complete conversion of the corresponding propargylic alcohol as monitored by TLC (petroleum ether/ether = 1:1), the mixture was filtered off. Evaporation of the solvent and flash chromatography on silica gel (eluent: petroleum ether/ether = 1:1) afforded 1.582 g (68%) of **1a**: liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.95−4.83 (m, 2 H), 4.11−3.94 (m, 4 H), 2.14−1.98 (m, 2 H), 1.47−1.19 (m, 10 H), 0.82 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (CDCl$_3$, 75.4 MHz): δ 211.3 (d, J_{PC} = 6.3 Hz), 93.3 (d, J_{PC} = 187.1 Hz), 76.7 (d, J_{PC} = 15.8 Hz), 62.1 (d, J_{PC} = 6.3 Hz), 29.8 (d, J_{PC} = 7.2 Hz), 27.4 (d, J_{PC} = 5.4 Hz), 21.9, 16.1 (d, J_{PC} = 6.4 Hz), 13.6; ^{31}P NMR (121.5 MHz, CDCl$_3$) δ 19.3; MS (*m*/*z*) 233 (M$^+$ + 1, 100); IR (neat) 1942, 1255, 1026 cm^{-1}; HRMS *m*/*z* (MALDI) calcd for C$_{11}$H$_{22}$O$_3$P$^+$ [M$^+$ + H] 233.1301, found 233.1308.

Pd-Catalyzed Addition Reaction of 1,2-Allenylphosphonates with Organoboronic Acids. Diethyl (2-Phenylhept-2(*E*)-en-3-yl)phosphonate (*E*-3aa). Typical Procedure II. Compounds **1a** (58 mg, 0.25 mmol) and **2a** (61 mg, 0.50 mmol) were added under nitrogen atmosphere to a solution of Pd(PPh$_3$)$_4$ (29 mg, 0.025 mmol) and AcOH (14 μL, 0.25 mol) in THF (3 mL). The resulting mixture was stirred at rt and monitored by TLC (ether). After evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether/ether = 1:1) to afford 63 mg (81%) of *E*-**3aa**: liquid; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31−7.17 (m, 3 H), 7.02 (d, J = 6.9 Hz, 2 H), 4.12−4.03 (m, 4 H), 2.27 (d, J = 3.6 Hz, 3 H), 2.04−1.92 (m, 2 H), 1.36−1.22 (m, 8 H), 1.08−0.96 (m, 2 H), 0.63 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (CDCl$_3$, 75.4 MHz) δ 153.6 (d, J_{PC} = 12.7 Hz), 143.4 (d, J_{PC} = 22.2 Hz), 128.1, 126.5 (d, J_{PC} = 172.0 Hz), 126.8, 126.4 (d, J_{PC} = 1.7 Hz), 61. 0 (d, J_{PC} = 5.7 Hz), 32.1 (d, J_{PC} = 1.3 Hz), 31.4 (d, J_{PC} = 12.0 Hz), 24.6 (d, J_{PC} = 7.5 Hz), 22.4, 16.2 (d, J_{PC} = 7.2 Hz), 13.4; ^{31}P NMR (121.5 MHz, CDCl$_3$) δ 22.5; MS (*m*/*z*) 310 (M$^+$, 96.59), 129 (100); IR (neat) 1615, 1597, 1575, 1490, 1441, 1241, 1025 cm^{-1}; HRMS *m*/*z* (MALDI) calcd for C$_{17}$H$_{28}$O$_3$P$^+$ (M$^+$ + H) 311.1771, found 311.1771.

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Supporting Information Available: Experimental details for all products not listed in the text and ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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