Palladium- and Nickel-Catalyzed Coupling Reactions of α-Bromoalkenylphosphonates with Arylboronic Acids and Lithium Alkenylborates

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Abstract: The coupling reaction of the α-bromoalkenylphosphonates with organoboranes was investigated. The palladium-catalyzed arylation took place successfully with arylboronic acids, while alkenylation proceeded with lithium alkenylborates and a nickel catalyst. In addition, an intramolecular Diels–Alder reaction of the diene prepared by the alkenylation afforded the corresponding adduct.

Keywords: boranes; borates; cross-coupling; nickel; palladium; phosphonates

Introduction

Substitution of a carboxylic acid unit by a phosphonic acid moiety in biologically active organic compounds is a promising strategy for increasing the potency and/or selectivity of the original activity. The alkenylphosphonic acids listed in Figure 1 are successful examples of this strategy.[1] These alkenylphosphonic (or -ate) groups can be constructed by several reactions[2] such as metal-catalyzed coupling reactions of alkenyl halides with $HP(O)(OR)_2$,[3] and $P(OR)_3$,[4] rhodium-catalyzed addition of $HP(O)(OR)_2$ to acetylenes,[5] Heck reaction of vinylphosphonates,[6] Wittig- and aldol-type reactions of aldehydes with methylphosphonates,[7] isomerization of allylphosphonates,[8] etc.[9]

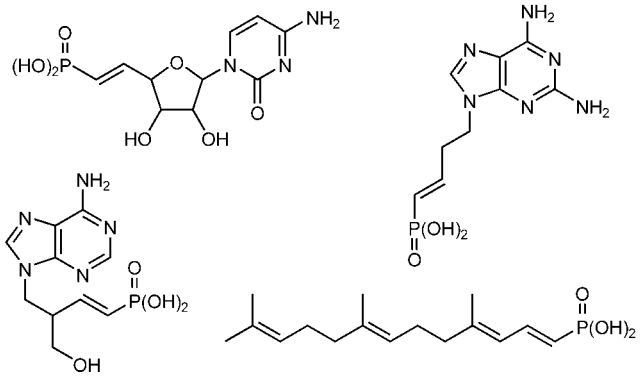

Figure 1. Biologically active alkenylphosphonic acid derivatives.

These reactions allow the synthesis of the β-monoalkyl-substituted alkenylphosphonates, but are hardly suitable for more substituted alkenylphosphonates, which would be intermediates for advanced complex analogues. Methods for obtaining such phosphonates have recently appeared,[10] however, they suffer from low efficiency in some cases and/or limited access to the specific compounds or to the olefin stereoisomers. With the fact that simple alkenylphosphonates are available easily,[3–9] we envisioned the transformation presented in Scheme 1. The first stage is bromination and dehydrobromination of alkenylphosphonate **A** to afford α-bromoalkenylphosphonate **B**, and the second stage is transition metal-catalyzed coupling reaction of **B** with aryl- or alkenylmetals. Since the influence of the phosphonate group on the coupling reaction has not been studied except for reactions with the reverse combination (α-metallic alkenylphosphonates with halides),[10d, e] several coupling reagents such as organoboranes, -borates, and -zincs were chosen for our investigation. Suzuki–Miyaura coupling[11,12] of **B** with arylboronic acid/Pd catalyst proceeded efficiently to produce α-aryl-substituted alkenylphosphonate **C**. On the other hand, alkenylation was achieved with the lithium alkenylborate/Ni catalyst, which was developed by us recently.[13,14] The products **C** could be precursors of the phosphonic acid versions of the α-arylalkanoic acids,[15] while dienes **D** are advanced intermediates for further transformation.[10a, b,16] The intramolecular Diels–Alder reaction of dienes **D** was also studied.[17]

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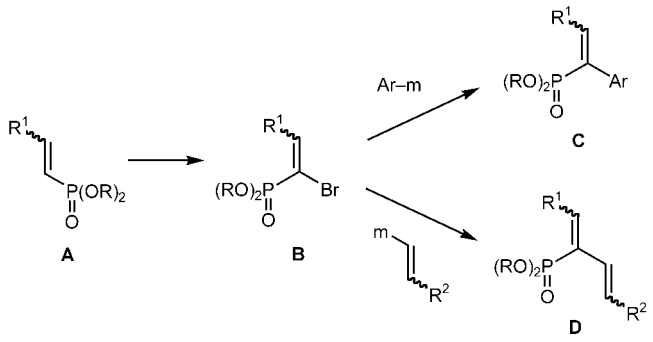
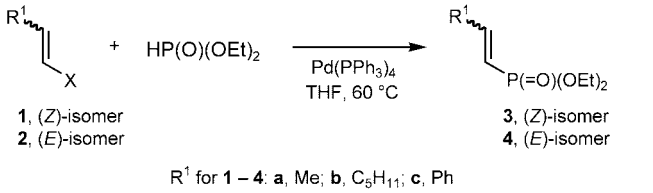


Scheme 1. Carbon-carbon bond formation at the α-position of alkenylphosphonates.

Results and Discussion

Synthesis of α-Bromoalkenylphosphonates

(*Z*)- and (*E*)-alkenylphosphonates **3a**–**c** and **4a**–**c** with Me, C_5H_{11}, and Ph groups as R^1 were selected as compounds **A** and were prepared from the corresponding (*Z*)- and (*E*)-alkenyl halides **1** and **2** by the procedure of Hirao[3] who originally carried out the phosphorylation of alkenyl halides with $HP(O)(OEt)_2$ using $Pd(PPh_3)_4$ as a catalyst at 90 °C in toluene. We modified the conditions for coupling between $HP(O)(OEt)_2$ (1 equiv.) and (*Z*)-propenyl bromide **1a** (1.2 equivs.) in order to prevent loss of the volatile bromide **1a** [Eq. (1)].[18] Thus, reaction at 60 °C in THF for 12 h produced the (*Z*)-propenylphosphonate **3a** stereospecifically in 90% yield (Table 1, entry 1). The modified conditions were also successful with (*Z*)- and (*E*)-alkenyl bromides, thus furnishing the alkenylphosphonates **3b**, **c** and **4a**–**c** in good to high yields (entries 2–6). Probably due to the steric reason, (*E*)-isomers **2a**–**c** produced higher yields of **4a**–**c** than (*Z*)-isomers **1a**–**c**. The olefinic geometries of the products were established by the coupling constants between the olefinic protons in the ^1H NMR spectra: $J = 13–14$ Hz and $J = ca.$ 17 Hz were observed for (*Z*)-isomers **3a**–**c** and (*E*)-isomers **4a**–**c**, respectively. The vicinal P–H coupling constants also supported the stereochemistries of **3a**, **b** and **4a**, **b**. The values, $J_{P,H} = 53$ Hz for **3a**,**b** and $J_{P,H} = 22$ Hz for **4a**, **b**, are consistent with literature values for *trans* and *cis* relationships of vicinal P and H atoms, respectively.[10f,19]



(1)

Table 1. Preparation of alkenylphosphonates **3** and **4**.[a]

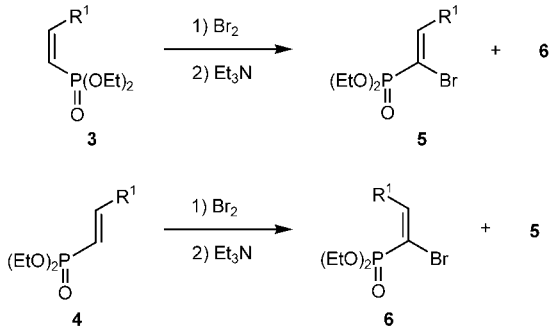
Entry	Substrate			Product	
	No.	X	R^1	No.	Yield [%]
1	**1a**	Br	Me	**3a**	90
2	**1b**	I	C_5H_{11}	**3b**	73
3	**1c**	I	Ph	**3c**	80
4	**2a**	Br	Me	**4a**	92
5	**2b**	I	C_5H_{11}	**4b**	91
6	**2c**	I	Ph	**4c**	87

[a] Reactions between $HP(O)(OEt)_2$ (1 equiv.) and alkenyl halides (1.2 equivs.) were carried out with $Pd(PPh_3)_4$ (5 mol %) and Et_3N (1 equiv.) at 60 °C for 12 h in THF.

Table 2. Preparation of α-bromoalkenylphosphonates **5** and **6**.

Entry	R^1	Alkenes	Product and yield [%][a, b]	
			5	**6**
1	Me	**3a**	**5a**, 61	–[c]
2	C_5H_{11}	**3b**	**5b**, 73	–[c]
3	Ph	**3c**	**5c**, 45	**6c**, 30
4	Me	**4a**	**5a**, 12	**6a**, 58
5	C_5H_{11}	**4b**	**5b**, 17	**6b**, 60
6	Ph	**4c**	**5c**, 31	**6c**, 47

[a] Separated by chromatography on silica gel.
[b] Isolated yields.
[c] Stereoisomer was not detected by ^1H NMR spectroscopy and TLC analysis.

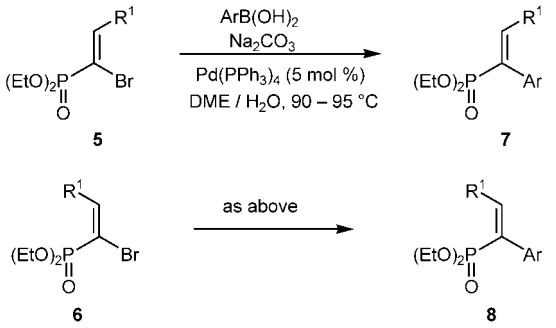


Scheme 2. Preparation of α-bromoalkenylphosphonates. R^1 for **3**–**6**: **a**, Me; **b**, C_5H_{11}; **c**, Ph.

Bromination of these alkenylphosphonates **3a**–**c** and **4a**–**c** with Br_2 proceeded at 10 °C to room temperature to produce the crude bromine adducts, which underwent dehydrobromination with Et_3N at 40 °C in CH_2Cl_2 to afford bromides **5a**–**c** from **3a**–**c** and **6a**–**c** from **4a**–**c**, respectively, in good yields (Scheme 2, Table 2). Although *anti* addition of Br_2 followed by *anti* elimination of HBr was the major stereochemical course, stereoselectivity varied from quite high (entries 1 and 2) to moderate (en-

tries 3–6) depending on the substituent R^1 and the olefin stereochemistry. Fortunately, differences in R_f values of the products were large enough to allow easy separation of the stereoisomers by chromatography on silica gel.[20]

The stereochemistries of the α-bromoalkenylphosphonates **5a–c** and **6a–c** were unambiguously determined by the vicinal P–H coupling constants in the ^{1}H NMR spectra of the *P*-C(Br)=C*H*R^1 part. Coupling constants $J = 14–16$ Hz observed for **5a–c** and $J = 38–40$ Hz for **6a–c** were decisive of the *cis* and *trans* relations between the vicinal P and H atoms, respectively.[19]



Scheme 3. Arylation of α-bromoalkenylphosphonates. R^1 for **5–8**: **a**, Me; **b**, C_5H_{11}; **c**, Ph.

Arylation of α-Bromoalkenylphosphonates

The palladium-catalyzed coupling reaction of the α-bromoalkenylphosphonates **5a–c** and **6a–c** was investigated with arylboronic acids, which are reagents of high reactivity as established by Suzuki and Miyaura (Scheme 3).[11,12] The results are presented in Table 3. Phenylation of (*Z*)-alkenyl bromide **5a** with $PhB(OH)_2$ (1.2 equivs.) in a trial experiment under the conditions reported by Gueiffier[21] with $Pd(PPh_3)_4$ (5 mol %) and Na_2CO_3 (1 equiv.) at 90–95 °C for 5 h in DME proceeded without any difficulty (entry 1). Product **7a** isolated in 93% yield was free of the stereoisomer **8a** by ^{1}H NMR spectroscopy and TLC analysis. Other boronic acids, *p*-$MeC_6H_4B(OH)_2$ and *p*-$MeOC_6H_4B(OH)_2$, showed similar reactivity to $PhB(OH)_2$ to provide **7b** and **7c** in good yields (entries 2 and 3). Likewise, *p*-$(CH_2{=}CH)C_6H_4B(OH)_2$ produced **7d** in 81% yield (entry 4), which is a new monomer in polymer science. Other alkenyl bromides **5b** and **5c** with the more bulky C_5H_{11} and Ph substituents as R^1 also produced the phenylation products **7e** and **7f**, respectively, in good yields with retention of the olefin stereochemistry (entries 5 and 6).

Next, the (*E*)-isomers **6a–c**, which are sterically less congested than the (*Z*)-isomers **5a–c**, were subjected to the coupling reaction. Under the same reaction conditions used for the (*Z*)-isomers, phenylation with $PhB(OH)_2$ proceeded well with retention of the olefin geometry to afford **6a–c** in high yields (Table 3, entries 7–9).

Olefin stereochemistry of the products **7a–f** and **8a**, **b** was determined by the vicinal P–H coupling constants in the ^{1}H NMR spectra, which were 23–24 Hz for **7a–f** and 48 Hz for **8a**, **b**, thus indicating *(E)*- and (Z)-stereochemistries for the olefins, respectively.[19] In the case of **8c**, the (*Z*)-geometry was determined on the basis of the different pattern of signals from that of **7f** of (*E*)-geometry, which was assigned by the $J_{P,H}$ value, because signals of the decisive proton overlapped with those of other protons.

α-Aryl-substituted alkenylphosphonates have been synthesized by Srebnik by hydroboration of alkynylphosphonates followed by palladium-catalyzed coupling with aryl halides.[10d] This method is, however, restricted to the production of (*Z*)-isomers **8** and suffers from low to moderate yields of 20–72%. In contrast, the present method covers the production of both isomers (**7** and **8**) in high yields.

Table 3. Arylation of α-bromoalkenylphosphonates **5** and **6**.

Entry	Substrate	R^1	Ar	Product, Yield [%][a]
1	**5a**	Me	Ph	**7a**, 93
2	**5a**	Me	*p*-MeC_6H_4	**7b**, 89
3	**5a**	Me	*p*-$MeOC_6H_4$	**7c**, 91
4	**5a**	Me	*p*-$(CH_2{=}CH)C_6H_4$	**7d**, 81
5	**5b**	C_5H_{11}	Ph	**7e**, 98
6	**5c**	Ph	Ph	**7f**, 90
7	**6a**	Me	Ph	**8a**, 95
8	**6b**	C_5H_{11}	Ph	**8b**, 94
9	**6c**	Ph	Ph	**8c**, 93

[a] Isolated yields by chromatography on silica gel.

Alkenylation of α-Bromoalkenylphosphonates

We next studied alkenylation of (*Z*)-alkenylphosphonate **5a** (R^1 = Me) with (*E*)-heptenylboronic acid (**9**), which was selected as a representative alkenylboronic acid. Unfortunately, reaction did not proceed under the arylation conditions described above, and resulted in recovery of **5a**. An attempted reaction with zinc reagent **10** and $Pd(PPh_3)_4$ as a catalyst at room temperature to 50 °C in THF was also unsuccessful, producing a complex mixture. These results are consistent with the less reactive nature of α-iodoenones in the coupling reaction.[22]

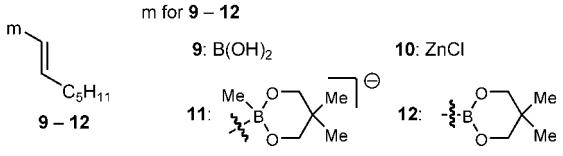


Table 4. Alkenylation of α-bromoalkenylphosphonates with alkenylborate **11**.[a]

Entry	R^1	Substrate	Conditions	Product and yield [%][b, c]	
				13	**14**
1	Me	**5a**	40 °C, 3 h	**13a**, 59	**14a**, 17
2	C_5H_{11}	**5b**	40 °C, 2 h	**13b**, 57	**14b**, 19
3	Ph	**5c**	40 °C, 2 h	**13c** or **14c**, 57	
4	Me	**6a**	rt., 3 h	**13a**, 20	**14a**, 66
5	C_5H_{11}	**6b**	rt., 3 h	**13b**, 20	**14b**, 74
6	Ph	**6c**	rt., 3 h	**13c** or **14c**, 65	

[a] Carried out with $NiCl_2$(dppf) (10 mol %) in THF.
[b] Separated by chromatography.
[c] Isolated yields.

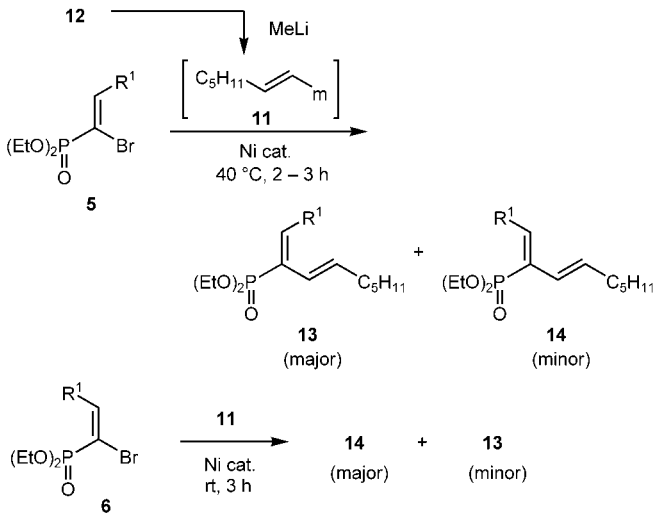
We have recently developed a highly reactive system of borates and a Ni catalyst for coupling reactions[13] with sterically congested 1-bromo-1-alkenes[14] and with secondary allylic esters.[23] This reagent system was applied to the alkenylation with **5a**. Thus, MeLi (1.5 equivs.) was added to a mixture of boronate ester **12**[14a] (1.5 equivs.) and $NiCl_2$(dppf) (10 mol %) in THF to generate lithium borate **11** and an active Ni(0) catalyst. Reaction of **5a** (1 equiv.) with the mixture was slow at room temperature, but proceeded at 40 °C efficiently to afford diene **13a** (R^1 = Me) in 59% yield accompanied by stereoisomer **14a** (R^1 = Me) in 17% yield (Scheme 4; Table 4, entry 1). The dienes were easily separated by chromatography on silica gel because of the large difference in R_f values between **13a** and **14a** [ΔR_f = 0.17, hexane/EtOAc (2:3)].

Similarly, reaction of alkenyl bromide **5b** ($R^1 = C_5H_{11}$) with borate **11** under the above conditions afforded **13b** and **14b** in 57% and 19% yields, respectively, after chromatography (ΔR_f = 0.17) (entry 2). In contrast to the (*Z*)-bromides **5a** and **5b**, the less congested (*E*)-isomers **6a** and **6b** underwent coupling with **11** at room temperature giving **14a** (R^1 = Me) and **14b** ($R^1 = C_5H_{11}$) as the major products (entries 4 and 5).

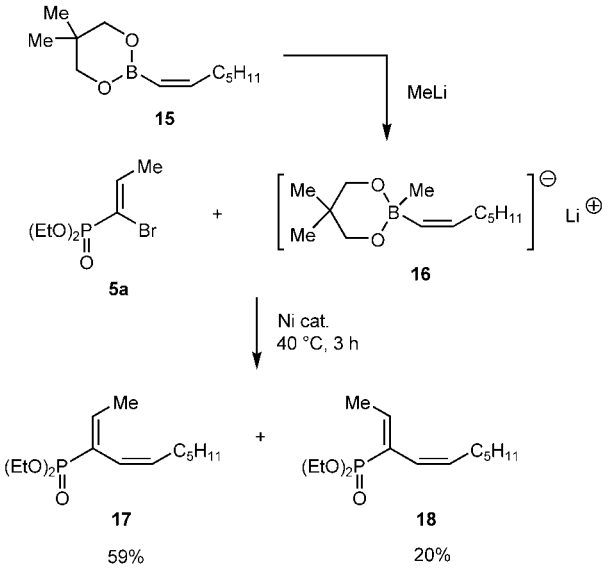
In contrast to the above bromides **5a**,**b** and **6a**,**b**, the coupling reaction of (*Z*)-alkenyl bromide **5c** (R^1 = Ph) with borate **11** afforded a single product of the unidentified olefin geometry at the PC=C(H)Ph unit in 57% yield (entry 3). The same product was produced as a sole product from (*E*)-isomer **6c** as well (entry 6).

With the protocol for the alkenyl coupling in hand, we next studied the reaction of (*Z*)-olefin **5a** (R^1 = Me) with (*Z*)-borate **16**[14a] (Scheme 5). Both olefin **5a** and borate **16** are sterically more congested than the corresponding stereoisomers. Nevertheless, the coupling did proceed cleanly at 40 °C to produce diene **17** in 59% yield along with the isomer **18** in 19% yield after chromatography (ΔR_f = 0.15) (Scheme 5).

The olefin stereochemistry in the coupling products **13a**, **b**, **14a**, **b**, **17**, and **18** was determined unambiguously on the basis of the vicinal coupling constants in the



Scheme 4. Alkenylation of bromides **5** and **6** with (*E*)-alkenylborate **11**. R^1 for **5**, **6**, **13**, **14**: **a**, Me; **b**, C_5H_{11}; **c**, Ph.



Scheme 5. Alkenylation of a more congested combination.

^{1}H NMR spectra, which are consistent with literature values for the olefin isomers (Figure 2).[19] However, overlap of proton Ha and the aromatic protons in **13c** or **14c** (derived from **5c** and **6c**) prevented determination of the $J_{P,Ha}$.

Diels–Alder Reaction of the Dienes

The alkenyl coupling products are electron-poor dienes and Diels–Alder reaction of these dienes attracts much attention. We synthesized diene **21** and examined the intramolecular Diels–Alder reaction of **25** derived from **21** through alcohol **22** (Scheme 6).

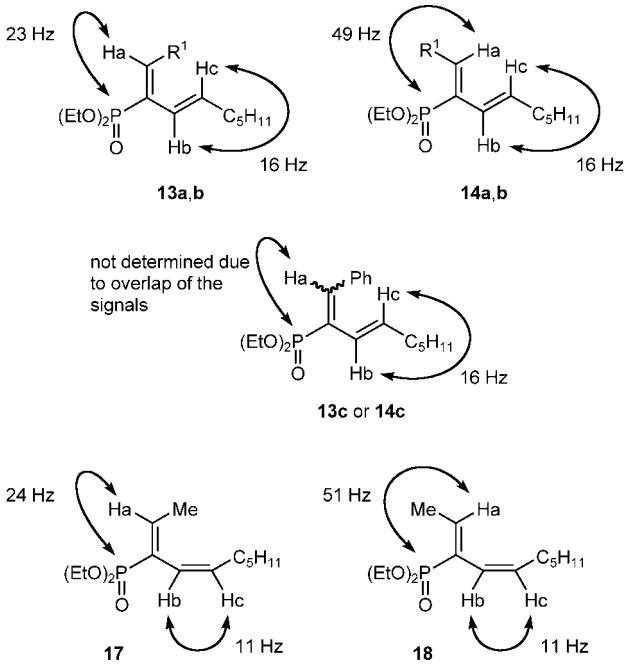
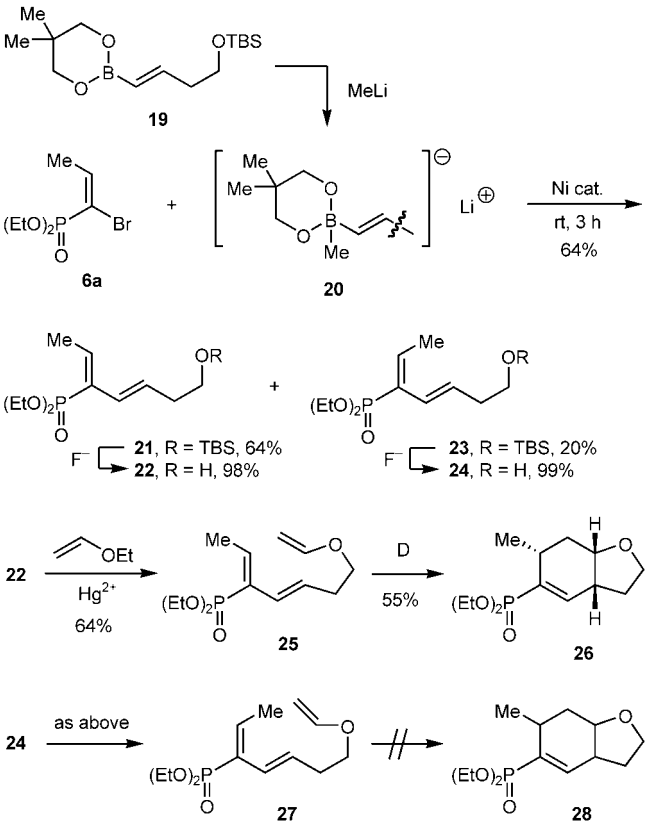


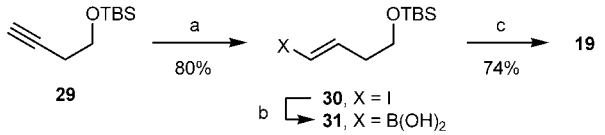
Figure 2. Coupling constants of dienes. R^1: **a**, Me; **b**, C_5H_{11}, **c**, Ph.

The requisite boronate ester **19** was prepared from acetylene **29**, which was first converted into iodide **30** by hydrozirconation[24] followed by iodination in 80% yield (Scheme 7). Lithiation and subsequent reaction of the alkenyl anion with $B(O\text{-}i\text{-}Pr)_3$, according to the procedure of Brown,[25] afforded boronic acid **31** after hydrolysis. Finally, esterification with $Me_2C(CH_2OH)_2$ furnished **19** in 74% yield.

Coupling of the (*E*)-bromide **6a** with borate **20** derived from **19** and MeLi proceeded at room temperature to afford **21** and the stereoisomer **23** in 64% and 20% yields, respectively (Scheme 6). After separation of the products by chromatography, **21** was converted into vinyl ether **25** in good yield through **22**. The Diels–Alder reaction was carried out at 160–170 °C for 17 h to afford **26** in 55% yield. The stereochemistry of the product was tentatively assigned on the basis of the literature precedents for similar full-carbon structures.[26] On the other hand, the vinyl ether **27** derived from the stereoisomer **23** decomposed totally upon heating.



Scheme 6. Synthesis of dienes and their Diels–Alder reaction.



Scheme 7. Synthesis of boronate ester **19**. (a) Cp_2ZrCl_2, $LiBHEt_3$ then I_2; (b) (i) *n*-BuLi, (ii) $B(O\text{-}i\text{-}Pr)_3$, (iii) H_2O; (c) $Me_2C(CH_2OH)_2$, $MgSO_4$.

Conclusion

We have synthesized functionalized α-bromoalkenylphosphonates in good yields and utilized them successfully in the Suzuki–Miyaura coupling reaction with arylboronic acids/Pd catalyst. We have also studied the alkenylation of α-bromoalkenylphoshonates, which proceeded with (*E*)- as well as (*Z*)-alkenylborates/Ni catalyst. The products obtained from these coupling reactions are a new class of phosphonates with unique structures and functionalities which we hope will be useful in the pharmaceutical field as well as in the field of polymer science as building blocks for complex phosphonates.

Experimental Section

General Remarks

The ^1H NMR spectra were taken in $CDCl_3$ at 300 MHz otherwise unless noted. The ^{31}P MR spectra were measured in $CDCl_3$ at 121.5 MHz. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). An ethereal solution of MeLi (1.0 M) was prepared from MeI and Li metal in

Et_2O, titrated, and stocked under argon atmosphere. Et_2O and THF were distilled from sodium benzophenone ketyl. All reactions sensitive to O_2 or moisture were conducted under argon atmosphere in dried flasks. Routinely, the products were extracted with appropriate solvents. The combined extracts were dried over $MgSO_4$ and, after concentration under vacuum, the crude products were purified by chromatography on silica gel using a mixture of hexane and EtOAc as eluent.

Typical Procedure for Phosphorylation: Synthesis of Diethyl (*Z*)-1-Propenylphosphonate (3a)

To a solution of *cis* bromide **1a** (1.12 mL, 13.0 mmol), $HP(O)(OEt)_2$ (1.40 mL, 10.9 mmol), and Et_3N (1.51 mL, 10.9 mmol) in THF (20 mL) was added $Pd(PPh_3)_4$ (627 mg, 0.543 mmol). The mixture was stirred at 60 °C for 12 h. After being cooled to 0 °C, the mixture was diluted with EtOAc and saturated $NaHCO_3$ (1:1, 30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were dried and concentrated to give an oil, which was purified by chromatography to furnish **3a**; yield: 1.74 g (90%); IR (neat): $\nu = 1628, 1250, 1027, 962\ cm^{-1}$; ^1H NMR $\delta = 1.33$ (t, $J = 7$ Hz, 6H), 2.09 (dq, $J = 7$, 1.5 Hz, 3H), 4.09 (dq, $J = 7.5$, 7 Hz, 4H), 5.61 (ddq, $J = 20$, 13, 1.5 Hz, 1H), 6.58 (ddq, $J = 53$, 13, 7 Hz, 1H); ^{31}P NMR: $\delta = 17.0$; anal. calcd. for $C_{12}H_{17}O_3P$: C 59.99, H 7.13; found: C 60.21, H 7.43.

Brief experimental procedures for and the spectral data of **3b**, **c** and **4a**–**c** are presented in the Supporting Information.

Typical Procedure for the α-Bromoalkenylphosponates: Synthesis of Diethyl (*Z*)-1-Bromo-1-propenylphosphonate (5a)

To an ice-cold solution of **3a** (1.93 g, 10.84 mmol) in CCl_4 (25 mL) was added dropwise bromine (0.62 mL, 12 mmol). The resulting solution was stirred at room temperature for 1.5 h. After being cooled to 0 °C, the reaction was quenched with aqueous $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined extracts were dried and concentrated to afford the bromine adduct, which was used as such for the next reaction. ^1H NMR: $\delta = 1.38$ (t, $J = 7$ Hz, 6H), 1.87 (d, $J = 7$ Hz, 3H), 4.13 (dd, $J = 13$, 4 Hz, 1H), 4.18–4.34 (m, 4H), 4.51–4.64 (m, 1H).

To an ice-cold solution of the above bromine adduct (3.64 g) in CH_2Cl_2 (25 mL) was added dropwise Et_3N (3.02 mL, 21.7 mmol). The resulting solution was stirred at 40 °C for 3 h. After being cooled to 0 °C, the solution was poured into 1 N HCl with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried, and concentrated to afford an oil, which was purified by chromatography to furnish *cis* bromide **5a**; yield: 1.70 g (61%). IR (neat): $\nu = 1623, 1252, 1022, 973\ cm^{-1}$; ^1H NMR δ 1.36 (dt, $J = 1$, 7 Hz, 6H), 1.95 (dd, $J = 6.5$, 3 Hz, 3H), 4.00–4.23 (m, 4H), 7.24 (dq, $J = 14$, 6.5 Hz, 1H); ^{31}P NMR: $\delta = 9.3$.

Brief experimental procedures for and the spectral data of **5b**, **c** and **6a**–**c** are presented in the Supporting Information.

Typical Procedure for Arylation: Synthesis of Diethyl (*E*)-1-Phenyl-1-propenylphosphonate (7a)

To a solution of **5a** (100 mg, 0.389 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) in DME (5 mL) were added $PhB(OH)_2$ (57 mg, 0.47 mmol) and aqueous Na_2CO_3 (41 mg, 0.39 mmol) in H_2O (1 mL). The mixture was stirred at 90–95 °C for 5 h and cooled to room temperature. Brine and EtOAc were added to the mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc twice. The combined extracts were dried and concentrated to afford an oil, which was purified by chromatography (hexane/EtOAc) to furnish **7a**; yield: 92 mg (93%). IR (neat): $\nu = 1250, 1025, 963\ cm^{-1}$; ^1H NMR: $\delta = 1.25$ (t, $J = 7$ Hz, 6H), 1.73 (dd, $J = 7$, 3.5 Hz, 3H), 3.98–4.14 (m, 4H), 6.98 (dq, $J = 23$, 7 Hz, 1H), 7.18–7.40 (m, 5H); ^{31}P NMR: $\delta = 17.7$; anal. calcd. for $C_{13}H_{19}O_3P$: C 61.41, H 7.53; found: C 61.22, H 7.65.

Brief experimental procedures for and the spectral data of **7b**–**f** and **8a**–**c** are presented in the Supporting Information.

Typical Procedure for Alkenylation: Synthesis of Diethyl (*E*)-1-[(*E*)-1-Heptenyl]-1-propenylphosphonate (13a) and Diethyl (*Z*)-1-[(*E*)-1-Heptenyl]-1-propenylphosphonate (14a)

To an ice-cold solution of $NiCl_2$(dppf) (27 mg, 0.039 mmol) and *trans*-boronate ester **12** (122 mg, 0.58 mmol) in THF (5 mL) was added MeLi (0.58 mL, 1.0 M in Et_2O, 0.58 mmol), and the resulting dark brown solution was stirred at 0 °C for 10 min to prepare the solution of borate **11** and active nickel species. To this was added *cis*-bromide **5a** (100 mg, 0.389 mmol). The resulting solution was stirred at 40 °C for 3 h, cooled to 0 °C, and diluted with saturated $NaHCO_3$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried, and concentrated to afford an oil, which was purified by chromatography to furnish **13a**; yield: 63 mg (59%) and its isomer **14a**; yield: 18 mg (17%).

***trans* Phosphonate 13a:** IR (neat): $\nu = 1252, 1025, 969\ cm^{-1}$; ^1H NMR: $\delta = 0.86$ (t, $J = 7$ Hz, 3H), 1.19–1.45 (m, 12H), 1.86 (dd, $J = 7$, 3.5 Hz, 3H), 2.11 (q, $J = 7$ Hz, 2H), 3.90–4.12 (m, 4H), 6.02–6.15 (m, 1H), 6.15 (dd, $J = 24$, 16 Hz, 1H), 6.62 (dq, $J = 23$, 7 Hz, 1H); ^{31}P NMR: $\delta = 19.8$.

The spectral data of the minor isomer **14a** are presented in the Supporting Information.

Brief experimental procedures for and the spectral data of **13b**, diene (**13c** or **14c**), and **14a**, **b** are presented in the Supporting Information.

Reaction of 5a with 16

According to the typical procedure for the alkenylation, a mixture of *cis*-bromide **5a** (100 mg, 0.389 mmol), boronate ester **15** (122 mg, 0.58 mmol), MeLi (0.58 mL, 1.0 M in Et_2O, 0.58 mmol), and $NiCl_2$(dppf) (27 mg, 0.039 mmol) in THF (5 mL) was stirred at 40 °C for 3 h to furnish **17**; yield: 62 mg (59%) and its isomer **18**; yield: 20 mg (19%).

***trans* Phosphonate 17:** IR (neat): $\nu = 1624, 1251, 1028, 962\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7$ Hz, 3H), 1.22–1.39 (m, 12H), 1.71 (ddd, $J = 7$, 3.5, 1.5 Hz, 3H),

1.82–1.93 (m, 2H), 3.92–4.12 (m, 4H), 5.62–5.78 (m, 2H), 6.69 (dq, $J=24$, 7 Hz, 1H); ^{31}P NMR: δ = 18.6. The multiplet at δ_H = 5.62–5.78 was resolved at 500 MHz ($CDCl_3$) into δ = 5.70 (ddt, $J=11$, 1, 6.5 Hz, 1H) and 5.76 (dm, $J=11$ Hz, 1H).

***cis* Phosphonate 18:** IR (neat): ν = 1249, 1026, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, $J=7$ Hz, 3H), 1.22–1.38 (m, 12H), 2.06–2.17 (m, 5H), 3.98–4.13 (m, 4H), 5.56 (dt, $J=11$, 7 Hz, 1H), 5.92 (dm, $J=11$ Hz, 1H), 6.31 (dq, $J=51$, 7 Hz, 1H); ^{31}P NMR: δ = 16.9.

(*E*)-{4-[(*tert*-Butyldimethylsilyl)oxy]-1-butenyl}-1,3,2-dioxaborolane (19)

To a flask containing Cp_2ZrCl_2 (3.49 g, 11.9 mmol) was added super hydride (11.9 mL, 1.0 M in THF, 11.9 mmol). After being stirred at room temperature in the dark for 2 h, acetylene **29** (1.0 g, 5.43 mmol) in THF (10 mL) was added. The mixture was stirred for additional 30 min and cooled to 0 °C. To this was added I_2 (1.65 g, 6.50 mmol). After 10 min of stirring, the reaction was quenched by addition of saturated $NaHCO_3$ and EtOAc (1:1, 10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried, and concentrated to afford an oil, which was purified by chromatography to furnish iodide **30**; yield: 1.35 g (80%).

To a solution of **30** (900 mg, 2.88 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (1.45 mL, 2.37 M in hexane, 3.44 mmol). After being stirred at −78 °C for 1 h, B(O-*i*-Pr)$_3$ (0.66 mL, 2.86 mmol) was added to the solution. The reaction was carried out for 2 h and quenched by pouring into saturated NH_4Cl. The mixture was extracted with EtOAc twice. The combined solutions of the crude boronic acid **31** were used for the next reaction without concentration.

To the solution of the crude boronic acid **31** were added $MgSO_4$ (0.35 g, 2.88 mmol) and 2,2-dimethyl-1,3-propanediol (329 mg, 3.16 mmol). After being stirred at room temperature for 12 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to afford an oil, which was purified by chromatography to furnish **19**; yield: 636 mg (74%). IR (neat): ν = 1640, 1476, 1415, 1256, 1093, 836, 776 cm^{-1}; ^{1}H NMR: δ = 0.04 (s, 6H), 0.88 (s, 9H), 0.96 (s, 6H), 2.31–2.44 (m, 2H), 3.62 (s, 4H), 3.68 (t, $J=7$ Hz, 2H), 5.40 (dt, $J=18$, 1.5 Hz, 1H), 6.50 (dt, $J=18$, 7 Hz, 1H).

Diethyl (*Z*)-1-[(*E*)-4-Hydroxy-1-butenyl]-1-propenylphosphonate (22) and Diethyl (*E*)-1-[(*E*)-4-Hydroxy-1-butenyl)-1-propenylphosphonate (24)

To an ice-cold solution of $NiCl_2$(dppf) (27 mg, 0.039 mmol) and *trans*-boronate ester **19** (174 mg, 0.583 mmol) in THF (5 mL) was added MeLi (0.58 mL, 1.0 M in Et_2O, 0.583 mmol). The solution was stirred at 0 °C for 10 min to prepare borate **20**. To this was added *trans*-bromide **6a** (100 mg, 0.389 mmol) and the reaction was carried out at room temperature for 3 h. The mixture was cooled to 0 °C and diluted with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried, and concentrated to afford an oil, which was purified by chromatography to furnish **21**; yield: 90 mg (64%) and its isomer **23**; yield: 28 mg (20%), both of which were independently subjected to deprotection with Bu_4NF as follows.

To an ice-cold solution of **21** (90 mg, 0.248 mmol) in THF (5 mL) was added Bu_4NF (0.37 mL, 1.0 M in THF, 0.37 mmol). After being stirred at room temperature for 1 h, the solution was cooled to 0 °C and diluted with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 twice to afford an oily product, which was purified by chromatography to furnish *cis*-phosphonate **22**; yield: 60 mg (98%). IR (neat): ν = 3411, 1233, 1024, 969 cm^{-1}; ^{1}H NMR: δ = 1.33 (t, $J=7$ Hz, 6H), 2.12 (dd, $J=7.5$, 3.5 Hz, 3H), 2.10–2.22 (m, 1H), 2.35 (q, $J=6.5$ Hz, 2H), 3.67 (t, $J=6.5$ Hz, 2H), 3.98–4.18 (m, 4H), 5.95 (dt, $J=16$, 7 Hz, 1H), 6.12 (t, $J=16$ Hz, 1H), 6.52 (dq, $J=48$, 7 Hz, 1H); ^{31}P NMR: δ = 15.0.

Similarly, olefin isomer **23** was converted into alcohol **24** in 99% yield. IR (neat): ν = 3400, 1235, 1025, 970, 794 cm^{-1}; ^{1}H NMR: δ = 1.32 (t, $J=7$ Hz, 6H), 1.91 (dd, $J=7$, 3.5 Hz, 3H), 1.95–2.15 (m, 1H), 2.42 (q, $J=6.5$ Hz, 2H), 3.71 (t, $J=6.5$ Hz, 2H), 3.96–4.19 (m, 4H), 6.13 (dt, $J=16$, 7 Hz, 1H), 6.31 (dd, $J=27$, 16 Hz, 1H), 6.67 (dq, $J=23$, 7 Hz, 1H).

Diethyl (*Z*)-1-[(*E*)-4-Vinyloxy-1-butenyl]-1-propenylphosphonate (25)

A solution of **22** (200 mg, 0.805 mmol) and $Hg(OAc)_2$ (52 mg, 0.081 mmol) in ethyl vinyl ether (2 mL) was refluxed for 24 h, cooled to 0 °C, and diluted with aqueous K_2CO_3. The product was extracted with EtOAc twice to afford an oil, which was purified by chromatography to furnish **25**; yield: 143 mg (65%). IR (neat): ν = 1618, 1245, 1199, 1024, 968 cm^{-1}; ^{1}H NMR: δ = 1.29 (t, $J=7$ Hz, 6H), 2.10 (dd, $J=7.5$, 3.5 Hz, 3H), 2.42 (q, $J=7$ Hz, 2H), 3.70 (t, $J=7$ Hz, 2H), 3.94–4.18 (m, 6H), 5.93 (dt, $J=16$, 6.5 Hz, 1H), 6.08 (t, $J=16$ Hz, 1H), 6.42 (dd, $J=14$, 7 Hz, 1H), 6.49 (dq, $J=48$, 7.5 Hz, 1H).

Diels–Alder Reaction of 25

A solution of **25** (60 mg, 0.219 mmol) in toluene (5 mL) in a sealed tube was heated at 160–170 °C for 15 h. The solvent was removed under vacuum to afford an oil, which was purified by chromatography to furnish **26**; yield: 33 mg (55%). IR (neat): ν = 1243, 1025, 963 cm^{-1}; ^{1}H NMR: δ = 1.25 (d, $J=7$ Hz, 3H), 1.32 (t, $J=7$ Hz, 6H), 1.67–2.32 (m, 4H), 2.43–2.56 (m, 1H), 2.78–2.94 (m, 1H), 3.65–4.25 (m, 7H), 6.68 (dd, $J=23$, 2.5 Hz, 1H); ^{31}P NMR: δ = 20.1.

Diethyl (*E*)-1-[(*E*)-4-Vinyloxy-1-butenyl]-1-propenylphosphonate (27)

A solution of **24** (250 mg, 1.00 mmol) and $Hg(OAc)_2$ (65 mg, 0.101 mmol) in ethyl vinyl ether (2 mL) was refluxed for 24 h to furnish **27**; yield: 198 mg (72%). IR (neat): ν = 1617, 1249, 1199, 1025, 968 cm^{-1}; ^{1}H NMR: δ = 1.25 (t, $J=7$ Hz, 6H), 1.85 (dd, $J=7$, 3.5 Hz, 3H), 2.46 (q, $J=7$ Hz, 2H), 3.70 (t, $J=7$ Hz, 2H), 3.91–4.15 (m, 6H), 6.09 (dt, $J=16$, 7 Hz, 1H), 6.25 (dd, $J=26$, 16 Hz, 1H), 6.40 (dd, $J=14$, 7 Hz, 1H), 6.65 (dq, $J=23$, 7 Hz, 1H).

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