ORGANIC LETTERS

2002
Vol. 4, No. 24
4241−4244

Coupling Reactions of α-Bromoalkenyl Phosphonates with Aryl Boronic Acids and Alkenyl Borates

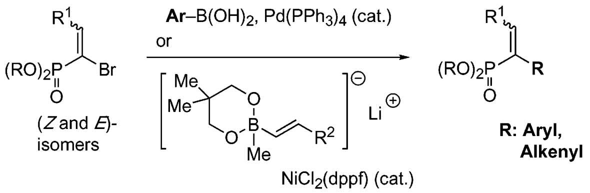
Yuichi Kobayashi* and Anthony D. William

*Department of Biomolecular Engineering, Tokyo Institute of Technology,
4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan*

ykobayas@bio.titech.ac.jp

Received August 20, 2002 *(Revised Manuscript Received October 21, 2002)*

ABSTRACT



Transition metal-catalyzed arylation and alkenylation of the α-bromoalkenyl phosphonates were investigated with organoboranes and -borates. Arylation was successful with the aryl boronic acids and a palladium catalyst, while alkenylation was found to proceed with alkenyl borates and a nickel catalyst. In addition, an intramolecular Diels–Alder reaction of the diene prepared by the alkenylation afforded the corresponding adduct.

Organo phosphonates have been used as substitutes of the corresponding esters and acids of high biological activity[1] and as convenient probes for designing antibodies on the basis of transition state models.[2] These investigations have been supported by organic synthesis; therefore, development of protocols for obtaining phosphonates of complex structures is inevitably important. However, investigation has been concentrated rather on phosphorylation of organic compounds such as alkynes, alkenes, and aldehydes, and hence C−C bond formation on simple phosphonates seems left behind. For example, alkenyl phosphonates with defined stereochemistry have been prepared by several methods[3] such as palladium-catalyzed coupling reaction of alkenyl halides and hydrogen phosphonates ($HP(O)(OR)_2$),[4] rhodium-catalyzed addition of hydrogen phosphonates to acetylenes,[5] and a Wittig-type reaction with methylenebisphosphonates,[6] etc.,[7] whereas 1,4-addition[8] and other reactions[9] of alkenyl phosphonates are reactions that have been reported so far. Herein,

---

(1) (a) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211−8213. (b) Kim, D. Y.; Rhie, D. Y. *Tetrahedron* **1997**, *53*, 13603−13608 and references therein.

(2) (a) Schultz, P.; Lerner, R. A. *Acc. Chem. Res.* **1993**, *26*, 391−395. (b) Stewart, J. D.; Liotta, L. J.; Benkovic, S. J. *Acc. Chem. Res.* **1993**, *26*, 396−404. (c) Cox, R. J.; Hadfield, A. T.; Mayo-Martín, M. B. *Chem. Commun.* **2001**, 1710−1711.

(3) Reviews: (a) Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333−349. (b) Minami, T.; Okauchi, T.; Kouno, R. *Synthesis* **2001**, 349−357.

(4) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909−913.

(5) Zhao, C.-Q.; Han, L.-B.; Goto, M.; Tanaka, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1929−1932.

(6) (a) Waszluc, W.; Janecki, T.; Bodalski, R. *Synthesis* **1984**, 1025−1027. (b) Aboujaoude, E. E.; Lietje, S.; Collignon, N. Teulade, M. P.; Savignac, P. *Tetrahedron Lett.* **1985**, *26*, 4435−4438. (c) Gupta, A.; Sacks, K.; Khan, S.; Tropp, B. E.; Engel, R. *Synth. Commun.* **1980**, *10*, 299−304.

(7) (a) Quntar, A. A. A.; Melman, A.; Srebnik, M. *Synlett* **2002**, 61−64. (b) Quntar, A. A. A.; Srebnik, M. *Org. Lett.* **2001**, *3*, 1379−1381. (c) Braga, A. L.; de Andrade, L. H.; Silveira, C. C.; Moro, A. V.; Zeni, G. *Tetrahedron Lett.* **2001**, *42*, 8563−8565. (d) Pergament, I.; Srebnik, M. *Tetrahedron Lett.* **2001**, *42*, 8059−8062. (e) Brunner, H.; Courcy, N. L. C.; Genet, J.-P. *Synlett* **2000**, 201−204. (f) Harnden, M. R.; Parkin, A.; Parratt, M. J. Perkins, R. M. *J. Med. Chem.* **1993**, *36*, 1343−1355. (g) Zhu, J.; Lu, X. *Tetrahedron Lett.* **1987**, *28*, 1897−1900. (h) Lu, X.; Zhu, J. *J. Organomet. Chem.* **1986**, *304*, 239−243. (i) Koizumi, T.; Tanaka, N.; Iwata, M.; Yoshii, E. *Synthesis* **1982**, 917−918.

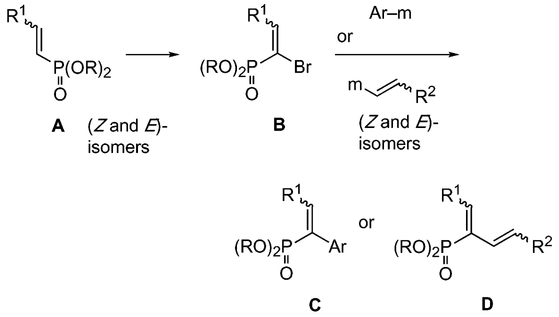
(8) (a) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591−11592. (b) Nagaoka, Y.; Tomioka, K. *Org. Lett.* **1999**, *1*, 1467−1469. (c) Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6428−6429. (d) Afarinkia, K.; Binch, H. M.; Modi, C. *Tetrahedron Lett.* **1998**, *39*, 7419−7422. (e) Junker, H.-D.; Fessner, W.-D. *Tetrahedron Lett.* **1998**, *39*, 269−272.

(9) (a) Kouno, R.; Tsubota, T.; Okauchi, T.; Minami, T. *J. Org. Chem.* **2000**, *65*, 4326−4332. (b) Kouno, R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1998**, *63*, 6239−6246.

10.1021/ol020167s CCC: $22.00

we report arylation and alkenylation of alkenyl phosphonates by a method summarized in Scheme 1. Products **C** would be precursors of the phosphonic acid version of α-aryl alkanoic acids,[10] while dienes **D** are advanced intermediates for further transformation.

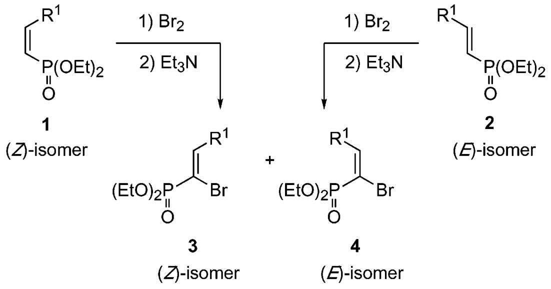
Scheme 1. Carbon−Carbon Bond Formation at the α-Position of Alkenyl Phosphonates



The key reaction is a transition metal-catalyzed coupling reaction of α-bromo compounds **B**, derived from alkenyl phosphonates **A**, with organometallics. Since information about the influence of the phosphonate group on the coupling reaction is limited to the reverse combination (α-phosphonoalkenyl boranes and stannanes with halides),[7c,9b] several coupling reagents such as organoboranes, -borates, and -zincs were chosen for the investigation. Aryl coupling proceeded efficiently with the aryl boronic acids. On the other hand, alkenylation was successful only with organoborates, which were developed by us recently. In addition, an intramolecular Diels−Alder reaction of compound **D** was studied.

Alkenyl phosphonates **1a**−**c** and **2a**−**c** with Me, C_5H_{11}, and Ph groups were selected as compounds **A** of Scheme 1 and prepared in good yields without contamination of the stereoisomers by the Hirao method[4] with modification.[11] As summarized in Scheme 2, bromination of these alkenyl phosphonates at 10 °C−rt followed by reaction of the crude bromine adducts with Et_3N at 40 °C in CH_2Cl_2 afforded bromides **3a**−**c** from **1a**−**c** and **4a**−**c** from **2a**−**c** in good yields (Table 1). Although anti addition of Br_2 followed by anti elimination of HBr was the major stereochemical course, stereoselectivity was varied from quite high (entries 1 and 3) to moderate (entries 5 and 6) depending on the substituent R^1 and the stereochemistry of the substrates.[12] Fortunately, large differences in R_f values[13] of the products allowed easy purification of the major products by routine chromatography on silica gel.

Scheme 2[a]



[a] R^1 for **1**−**4**: **a**, Me; **b**, C_5H_{11}; **c**, Ph.

Table 1. Preparation of α-Bromoalkenyl Phosphonates **3** and **4**

entry	R^1	substrate	products[a] and yields (%)[b] major	minor
1	Me	**1a**	**3a** (61)	
2	Me	**2a**	**4a** (58)	**3a** (12)
3	C_5H_{11}	**1b**	**3b** (73)	
4	C_5H_{11}	**2b**	**4b** (60)	**3b** (17)
5	Ph	**1c**	**3c** (45)	**4c** (30)
6	Ph	**2c**	**4c** (47)	**3c** (31)

[a] Separated easily by routine chromatography on silica gel. [b] Isolated yields.

Arylation of the α-bromoalkenyl phosphonates **3a**−**c** and **4a**−**c** was investigated with aryl boronic acids, which are well-established reagents of high reactivity.[14] The results are presented in Table 2.[12] Coupling was investigated first with (*Z*)-isomer **3a** (R^1 = Me), a sterically more congested isomer than the corresponding (*E*)-isomer **4a** due to the projection of R^1 (= Me) toward the reaction site. The phenylation of **3a** and $PhB(OH)_2$ proceeded successfully under the conditions reported[15] with $Pd(PPh_3)_4$ (5 mol %) and Na_2CO_3 (1 equiv) at 90−95 °C for 5 h in DME to furnish product **5a** in 93% yield (entry 1). No isomer of **5a** (i.e., **6a**) was detected by TLC analysis and ^1H NMR spectroscopy. Substrates **3b** and **3c** with the more bulky C_5H_{11} and Ph substituents as R^1 also produced the phenylation products **5e** and **5f**, respectively, in good yields with retention of the stereochemistry (entries 5 and 6). As for boronic acids, *p*-Me-C_6H_4-$B(OH)_2$ and *p*-MeO-C_6H_4-$B(OH)_2$ showed reactivity similar to that of $PhB(OH)_2$ in the reaction with **3a** to provide **5b** and **5c** in good yields (entries 2 and 3). Likewise, *p*-(CH_2=CH)-

---

[10] Goulioukina, N. S.; Dolgina, T. M.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 319−327 and references therein.

[11] Kobayashi, Y.; William, A. D.; Tokoro, Y. *J. Org. Chem.* **2001**, *66*, 7903−7906.

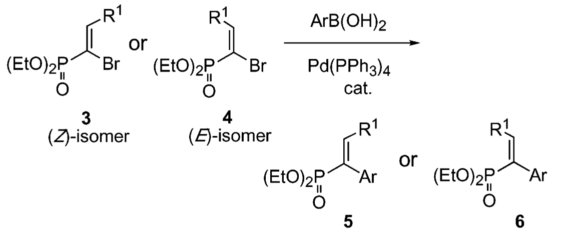
[12] Stereochemistry of the phosphonate group-attached olefin in compounds **3a**−**c**, **4a**−**c**, **5a**−**f**, **6a**−**c**, **10a**,**b**, **11a**,**b**, **13**, **16**, and **17** was determined by coupling counstants between vicinal H and P atoms in ^1H NMR spectra, which are given in Supporting Information. See ref 7a and the following refs for general information about coupling constants: (a) Kenyon, G. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 3557−3561. (b) Borowitz, I. J.; Yee, K. C.; Crouch, R. K. *J. Org. Chem.* **1973**, *38*, 1713−1718. (c) Teulade, M.-P.; Savignac, P. *J. Organomet. Chem.* **1986**, *304*, 283−300.

[13] R_f values of the products: **3a** = 0.26 and **4a** = 0.39 with 2:3 hexane/EtOAc; **3b** = 0.53 and **4b** = 0.66 with 2: 3 hexane/EtOAc; **3c** = 0.21 and **4c** = 0.26 with 1:1 hexane/EtOAc.

[14] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972−980.

[15] Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572−6575.

Table 2. Arylation of **3a**−**c** and **4a**−**c**



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

[a] Isolated yield.

C_6H_4-$B(OH)_2$ produced **5d** in 81% yield (entry 4), which is a new monomer in polymer science.

Next examined was phenylation of (*E*)-isomers **4a**−**c**, which under the same reaction conditions used for the (*Z*)-isomers proceeded smoothly to furnish **6a**−**c** in high yields (entries 7−9).

Recently, synthesis of α-aryl compounds of type **6** has been reported by Srebnik.[7d] This method is, however, restricted to production of (*Z*)-isomers **6** and suffers from moderate to low yields of 72−20%. On the contrary, the present method covers production of both isomers in high yields.

In contrast to the above arylation, alkenylation of **3a** with heptenylboronic acid (**7**) (Figure 1), which was selected as a representative alkenyl boronic acid, did not proceed under the arylation conditions described above and resulted in recovery of **3a**. Use of zinc reagent **8** and $Pd(PPh_3)_4$ as a catalyst at rt−50 °C in THF was also unsuccessful, producing a complex mixture.

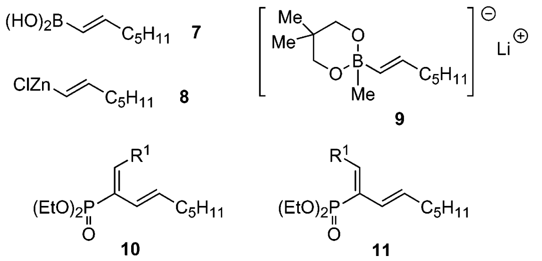


Figure 1. Alkenyl reagents **7**−**9** we examined for coupling with **3** and **4**; coupling products **10** and **11** were obtained from **9**.

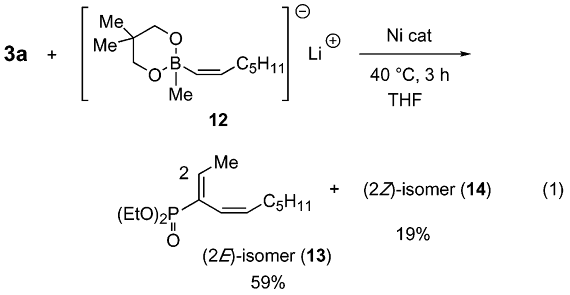
These results recall the less reactive nature of α-iodo enones to the coupling reaction.[16] After several fruitless reactions, borate **9**[17] with a nickel catalyst, a reagent system developed by us for coupling with sterically congested cis alkenyl bromides,[18] was found to furnish the coupling product **10a** (R^1 = Me). Although <20% was recorded under the original reaction conditions ($NiCl_2$(dppf), rt, THF), a slightly higher temperature of 40 °C raised the yield to 59% (Table 3, entry 1), though accompanied with stereoisomer **11a** (R^1 = Me) in 17% yield. Fortunately, **10a** and **11a** were easily separated by routine chromatography on silica gel because of the large difference in R_f values between **10a** and **11a** ($\Delta R_f = 0.17$ with 2:3 hexane/EtOAc). Similarly, **3b** afforded **10b** ($R^1 = C_5H_{11}$) and **11b** in 57 and 19% yields, respectively, with ΔR_f of 0.17 (entry 2). Reaction of less congested (*Z*)-isomers **4a** and **4b** proceeded at room temperature to afford **11a** (R^1 = Me) and **11b** ($R^1 = C_5H_{11}$) as the major products (entries 3 and 4).[19]

Table 3. Coupling Reaction of **3a**,**b** and **4a**,**b** with Alkenyl Reagent **9** and a Nickel Catalyst[a]

entry	R^1	substrate	conditions[b]	products[c] and yields (%)[d]	
1	Me	**3a**	40 °C, 3 h	**10a**, 59	**11a**, 17
2	C_5H_{11}	**3b**	40 °C, 2 h	**10b**, 57	**11b**, 19
3	Me	**4a**	rt, 3 h	**10a**, 20	**11a**, 66
4	C_5H_{11}	**4b**	rt, 3 h	**10b**, 20	**11b**, 74

[a] $NiCl_2$(dppf) (5−10 mol %). [b] THF was used as a solvent. [c] Separated easily by routine chromatography on silica gel. [d] Isolated yields.

The above protocol with a borate/Ni catalyst was extended to the sterically more congested borate **12**,[17] which furnished product **13**[12] in 59% yield with the isomer in 19% yield (ΔR_f = 0.15) (eq 1).



Recently, dienes of type **11** have been synthesized through zirconacycles.[7a] However, the present method is more flexible in providing other stereoisomers such as **10** and **13**, the latter of which is the most congested diene.

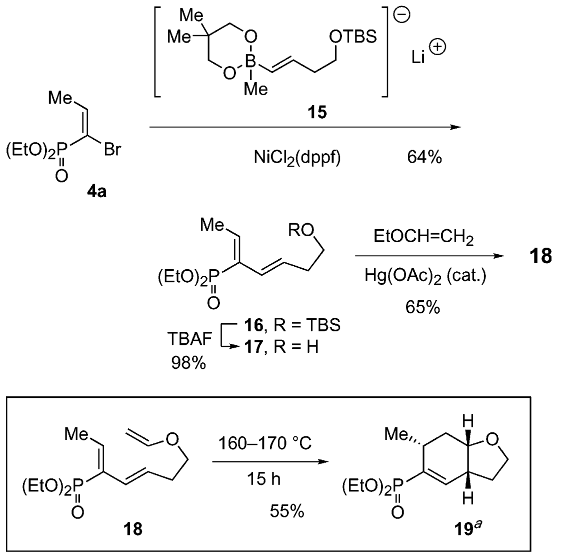
---

(16) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453−4456.

(17) Prepared from the corresponding boronate ester (structure not shown) and MeLi (THF, 0 °C, 10−15 min).

(18) (a) Kobayashi, Y.; Nakayama, Y.; Mizojiri, R. *Tetrahedron* **1998**, *54*, 1053−1062. (b) Nakayama, Y.; Kumar, G. B.; Kobayashi, Y. *J. Org. Chem.* **2000**, *65*, 707−715.

Scheme 3. Diels-Alder Reaction of Diene **18**



[a] Stereochemistry shown in the structure is that tentatively assigned.

The multifunctional groups of the products are attractive for further transformation to more complex compounds. Asymmetric hydroxylation, asymmetric hydrogenation, Diels−Alder reaction, and 1,4-addition are such reactions. Thus, we investigated briefly the intramolecular Diels−Alder reaction of **17**, which was prepared by coupling reaction between bromide **4a** and borate **15**[17] followed by deprotection of the TBS group and subsequent vinylation (Scheme 3). Diels−Alder reaction of **17** proceeded successfully at 160−170 °C in toluene for 15 h to produce adduct **18** in 55% yield.

In conclusion, we have shown arylation and alkenylation of α-bromoalkenyl phosphonates. The products are a new class of phosphonates with unique structures and functionalities and will be useful in fields such as pharmacology and polymer science.[20]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Typical experimental procedures, spectral data for all new compounds, and a list of alkenyl phosphonates with coupling constants used for determination of the olefin geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020167S

---

(19) Alkenylation of bormides **3c** and **4c** wtih **9** proceeded as well. However, products from **3c** and **4c** were identical by ^{1}H NMR spectroscopy and TLC analysis. Unfortunately, the stereochemistry of the trisubstituted olefin of the product could not be determined because of overlap of the signals.

(20) All new compounds were characterized by IR and ^{1}H NMR spectra.